NEURAL REGENERATION RESEARCH
Volume 7, Issue 18, June 2012
www.nrronline.org

Cite this article as: Neural Regen Res. 2012;7(18):1428-1435.

Five-year follow-up of 23 asymmetrical Parkinson's disease patients treated with unilateral subthalamic nucleus stimulation★

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Abstract

In this study, 23 asymmetrical Parkinson's disease patients were treated with unilateral deep brain stimulation of the subthalamic nucleus and followed up for 5 years. At 5 years after stimulation treatment, Unified Parkinson's Disease Rating Scale II, III and axial symptom scores in the off-drug condition were significantly increased compared those at baseline. However, total Unified Parkinson's Disease Rating Scale II, III and axial symptom scores were significantly lower with stimulation-on compared with the synchronous stimulation-off state in off-drug condition, and the motor symptoms of contralateral side limbs were effectively controlled. Only low Hoehn-Yahr stage was correlated with good long-term postoperative improvement in motor symptoms. The mean levodopa-equivalent daily dose after stimulation treatment was significantly lower than that before treatment, but dyskinesias became worse. Our experimental findings indicate that unilateral deep brain stimulation of the subthalamic nucleus is an effective treatment for improving motor symptoms in well selected asymmetrical Parkinson's disease patients presenting no severe axial symptoms and dyskinesias.

Key Words

Parkinson's disease; deep brain stimulation; subthalamic nucleus; neural regeneration

Abbreviations

PD, Parkinson's disease; DBS, deep brain stimulation; STN, subthalamic nucleus; UPDRS, Unified Parkinson's Disease Rating Scale

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Received: 2012-01-08
Accepted: 2012-04-23
(N20110107002/WJ)

Liang JC, Hu XW, Zhou XP, Jiang XF, Cao YQ, Wang LX, Jin AG, Liu JM. Five-year follow-up of 23 asymmetrical Parkinson's disease patients treated with unilateral subthalamic nucleus stimulation. Neural Regen Res. 2012;7(18):1428-1435.

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doi:10.3969/j.issn.1673-5374.2012.18.010

INTRODUCTION

Subthalamic nucleus (STN) deep brain stimulation (DBS) has become the most important neurosurgical therapy for advanced Parkinson's disease (PD)[1-4]. However, bilateral procedures are more time-consuming and invasive than unilateral procedures, and may be associated with increased risks of surgical and neurological complications and neuropsychological sequelae[5-9]. Recently, several studies have shown that unilateral STN DBS produces a significant improvement in advanced PD patients without the adverseness reported in studies of bilateral STN DBS[10-14]. However, the follow-up durations of most studies were only 3–12 months or the sample sizes were not large enough for statistical analysis. There are still two important questions in this field: (1) is unilateral STN DBS a long-term effective candidate therapy for advanced asymmetrical PD patients? (2) How can appropriate patients be selected to ensure good results and avoid unnecessary secondary operations? This study followed a prospective cohort study of 23 patients

with advanced asymmetrical PD who underwent chronic unilateral STN DBS for at least 5 years, aiming to explore the long-term efficacy and indications of unilateral STN DBS for advanced asymmetrical PD.

RESULTS

Quantitative analysis of patients

A series of 31 consecutive asymmetrical PD patients were involved in this study. Four patients died of other systemic diseases before the final assessment. Another four patients, who received contralateral STN DBS within 2–4 years of the original operation, were excluded as having had bilateral procedures. No patient withdrew or was lost to follow up. In total, 23 patients completed the follow-up period of at least 5 years with unilateral STN DBS treatment.

Baseline information of involved patients

The preoperative characteristics, Hoehn and Yahr (H&Y) staging scale scores and levodopa-equivalent daily doses (LEDDs) of these 23 patients are summarized in Table 1. Unified Parkinson's Disease Rating Scale (UPDRS) scores assessed at baseline are shown in Table 2.

Table 1 Baseline information on the 23 patients undergoing unilateral deep brain stimulation of subthalamic nucleus

Variable	Value
Sex (male/female, *n*)	18/5
Age (year)	60.6±6.4
Duration of symptomatic disease (year)	8.4±5.1
Right hand dominance	23
Deep brain stimulation side (left/right, *n*)	13/10
Preoperative Hoehn and Yahr stage (score)	2.6±0.5
Medication therapy (*n*)	23
Preoperative levodopa-equivalent daily dose (mg/d)	654.4±203.6

Measurement data are expressed as mean ± SD.

UPDRS improvement at 1-year follow-up

At 1 year postoperatively, compared with baseline, the UPDRS III scores were significantly increased in the stimulation-off state. However, in the stimulation-on state, the UPDRS II and III scores were significantly decreased by 28.98% and 36.22%, respectively, as were the resting tremor, rigidity and bradykinesia scores. Almost all contralateral motor symptoms were well controlled but the scores of most ipsilateral motor symptoms improved only a little. The total score for the axial part of UPDRS III decreased by 14.82%, and this decrease was non-significant. Only neck rigidity manifested a significant improvement.

Compared with the stimulation-off state at 1 year, the UPDRS II and III scores with stimulation-on were significantly lower, as were the scores for contralateral motor symptoms and neck rigidity, gait and rising from a chair, but the score for the axial part of UPDRS III was not significantly different.

UPDRS improvement at 5-year follow-up

At 5 years postoperatively, the total UPDRS II and III scores and the score for the axial part of UPDRS III, in the stimulation-off state, were significantly higher than those at baseline. In the stimulation-on state, the total UPDRS II score was 15.76% lower than that at baseline. The score for the axial part of UPDRS III was equal to that at baseline. The total UPDRS III score was significantly decreased by 27.46% compared with that at baseline. All contralateral motor symptoms, except action tremor, showed significant improvement, similar to the results at 1 year.

Compared with the stimulation-off state, total UPDRS II and III scores and the score for the axial part of UPDRS III in the stimulation-on state were lower by 37.37%, 41.14% and 26.91%, respectively, and all differences were significant. All contralateral motor symptoms were well controlled.

Prediction factors for improvement of UPDRS and second operation

The results of binary logistic regression analysis (backwards: conditional) are shown in Table 3. Only when both $B < -1$ or $B > 1$ and $P < 0.05$ were met, would the predictor be considered an effective prediction factor. Only surgical side and preoperation H&Y stage predicted improvement of UPDRS II score in the first year. No factors could reliably predict whether the patients would have to receive a second operation.

Further analysis of the usefulness of surgical side and H&Y stage as prediction factors for improvement

There were no significant differences in the degrees of improvements in UPDRS II and III scores at 1 and 5 years between procedure sides. At 1 year postoperation, although there was a trend toward lower H&Y stage being associated with better improvements, no significant difference was found between H&Y stages. At 5 years, lower H&Y stage was associated with significantly greater improvements in UPDRS II and III scores ($P < 0.05$). These results are shown in Figures 1 and 2.

UPDRS scores for the less affected side during 5-year follow-up

In all 27 surviving patients (including the 23 who underwent unilateral ST DBS and four who received contralateral STN DBS), at 5 years postoperatively, the mean motor score on the less affected side increased to 14.59 ± 5.09.

Table 2 Unified Parkinson's Disease Rating Scale (UPDRS) scores and *P* values with medication-off after unilateral deep brain stimulation of the subthalamic nucleus in 23 patients

Item	Score range	Preop	Off stimulation			
			1 yr	5 yr	*P* value	
					Off 1-yr *vs*. preop	Off 5-yr *vs*. preop
Total UPDRS-II score	0–52	17.39±6.32	19.04±6.73	23.39±6.52	0.350	0.005
Total UPDRS-III score	0–108	44.17±12.89	48.35±12.86	54.43±12.82	< 0.001[a]	< 0.001
Resting tremor	0–20	9.30±4.81	9.61±4.93	11.04±4.64	0.814	0.241
Action tremor[a]	0–8	0.65±1.85	0.70±1.26	1.04±1.26	0.888	0.208
Rigidity	0–20	8.35±4.72	9.09±5.01	10.91±4.59	0.552	0.041
Bradykinesia	0–36	16.91±7.03	18.61±6.81	19.61±5.82	0.388	0.171
Contralateral resting tremor	0–8	5.13±2.12	5.52±2.11	6.13±2.03	0.464	0.063
Contralateral action tremor	0–4	0.48±0.79	0.52±0.90	0.74±0.81	0.845	0.242
Contralateral rigidity	0–8	4.78±2.24	4.96±2.31	5.78±1.93	0.751	0.070
Contralateral bradykinesia	0–16	9.30±3.56	10.13±3.43	10.26±2.78	0.406	0.336
Ipsilateral resting tremor[a]	0–8	3.13±2.05	2.96±2.25	3.13±2.18	0.783	1.000
Ipsilateral action tremor[a]	0–4	0.17±0.49	0.17±0.49	0.30±0.63	1.000	0.363
Ipsilateral rigidity[a]	0–8	2.22±1.57	2.57±1.83	3.48±2.09	0.526	0.023
Ipsilateral bradykinesia[a]	0–16	5.70±3.15	6.13±2.03	7.00±2.11	0.615	0.133
Total axial score	0–24	8.57±3.99	10.04±3.88	11.78±3.41	0.197	0.005
Speech	0–4	1.52±0.95	1.65±0.93	1.70±0.88	0.638	0.530
Neck rigidity[a]	0–4	1.35±1.11	1.57±1.08	1.78±0.90	0.428	0.114
Posture	0–4	1.48±0.79	1.61±0.66	1.87±0.69	0.540	0.068
Gait	0–4	1.39±0.78	1.83±0.89	2.17±0.78	0.058	0.001
Postural stability	0–4	1.48±0.85	1.65±0.83	2.17±0.72	0.450	0.003
Rising from chair	0–4	1.35±0.98	1.74±1.01	2.09±0.95	0.133	0.005

Item	Score range	On stimulation					
		1 yr	5 yr	*P* value			
				On *vs*. off 1-yr	On *vs*. off 5-yr	On 1-yr *vs*. preop	On 5-yr *vs*. preop
Total UPDRS-II score	0–52	12.35±4.88	14.65±5.12	< 0.001	< 0.001	0.005	0.122
Total UPDRS-III score	0–108	28.17±12.46	32.04±11.76	< 0.001	< 0.001	< 0.001	< 0.001
Resting tremor	0–20	3.57±3.64	4.35±3.51	< 0.001	< 0.001	< 0.001	< 0.001
Action tremor[a]	0–8	0.26±0.62	0.39±0.78	0.163	0.037	0.208	0.401
Rigidity	0–20	4.30±3.25	5.17±3.01	< 0.001	< 0.001	0.001	0.012
Bradykinesia	0–36	11.83±7.14	12.61±6.32	0.001	0.001	0.011	0.030
Contralateral resting tremor	0–8	0.74±1.25	1.00±1.31	< 0.001	< 0.001	< 0.001	< 0.001
Contralateral action tremor	0–4	0.26±0.62	0.22±0.60	0.242	0.020	0.329	0.242
Contralateral rigidity	0–8	1.17±1.40	1.09±1.08	< 0.001	< 0.001	< 0.001	< 0.001
Contralateral bradykinesia	0–16	4.96±3.65	4.30±3.31	< 0.001	< 0.001	< 0.001	< 0.001
Ipsilateral resting tremor[a]	0–8	2.39±2.08	2.83±2.10	0.371	0.630	0.243	0.630
Ipsilateral action tremor[a]	0–4	0.04±0.21	0.17±0.49	0.363	0.363	0.363	1.000
Ipsilateral rigidity[a]	0–8	2.48±1.86	3.30±1.89	0.874	0.751	0.634	0.049
Ipsilateral bradykinesia[a]	0–16	5.09±2.92	6.39±2.69	0.229	0.482	0.482	0.422
Total axial score	0–24	7.30±3.15	8.61±3.23	0.063	0.030	0.561	0.503
Speech	0–4	1.39±0.94	1.35±0.98	0.347	0.211	0.638	0.530
Neck rigidity[a]	0–4	0.65±0.78	0.74±0.69	0.001	< 0.001	0.012	0.028
Posture	0–4	1.48±0.73	1.61±0.72	0.540	0.222	1.000	0.540
Gait	0–4	1.26±0.69	1.74±0.69	0.014	0.058	0.566	0.128
Postural stability	0–4	1.35±0.78	1.65±0.71	0.188	0.025	0.571	0.450
Rising from chair	0–4	1.17±0.65	1.52±0.73	0.031	0.031	0.502	0.502

Superscript a: test of homogeneity of variances. preop: Preoperation; yr: year; on: stimulation-on; off: stimulation-off.

The mean worsened motor score (the postoperation motor score minus the baseline) on the less affected side during the 5 years was 3.33 ± 4.24. The mean side difference (the motor score of more affected side subtract the motor score of less affected side) and mean side ratio (the motor score of more affected side divide by the motor score of less affected side) were 9.00 ± 2.37 and 1.76 ± 0.44, respectively (compared with 8.54 ± 2.36 and 1.92 ± 0.54 preoperatively). The motor symptoms on the less affected side were greatly worsened in nine cases (worsened motor score > 5, mean 7.77 ± 3.39). In six of the 27 patients, the motor scores for the less affected sides were > 19.70 (the mean preoperative motor score on the more affected side) at 5 years (Table 4).

Table 3 Prediction factors, and *B* and *P* values for Unified Parkinson's Disease Rating Scale (UPDRS) II & III scores at 1 and 5 years after surgery

		Predictors	*B*	*P*
1 year	UPDRS II	Side	−3.58	0.035
		Age of onset	0.31	0.063
		Hoehn and Yahr stage	−3.26	0.048
		Parkinson's disease duration	0.56	0.027
	UPDRS III	Motor score on the less affected side	−0.53	0.007
		Age	−3.89	1.000
		Age of onset	−3.94	1.000
		Parkinson's disease duration	−4.03	1.000
5 years	UPDRS II	Motor score on the less affected side	−0.22	0.094
		Levodopa-equivalent daily dose	−0.01	0.131
	UPDRS III	Age	−0.16	0.112
		Hoehn and Yahr stage	−2.37	0.087

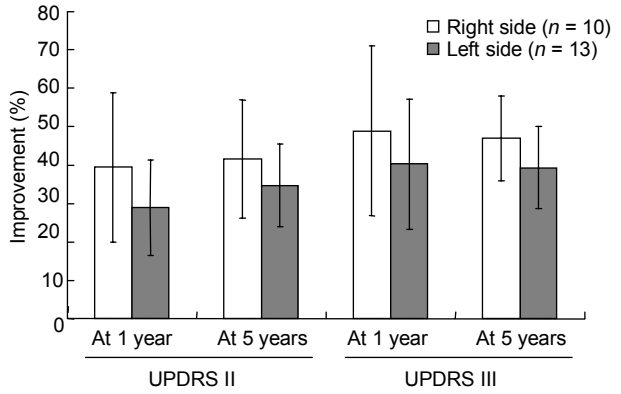

Figure 1 Improvements in Unified Parkinson's Disease Rating Scale (UPDRS) II & III scores at 1 and 5 years postoperatively analyzed by left- and right-side procedures.

Although right-side procedures always produced greater improvements in symptoms than left-side procedures, no significant difference was found between them with Student's *t*-test (*P* = 0.207, 0.143, 0.172, 0.208 respectively). Data are expressed as mean ± SD.

The improvement calculation was compared with baseline [$(1-\frac{UPDRS}{baseline})$×100%].

LEDD and levodopa-related complications reduced postoperatively

The average LEDD significantly decreased to 432.39 ± 211.99 mg per day (decreased by 33.92% compared with baseline, *P* < 0.01) at 1 year, but then increased to 491.30 ± 169.93 mg per day (decreased by 24.92% compared with baseline, *P* < 0.01) at 5 years postoperatively. With the decreasing dose of levodopa, the average off-duration period in the waking day significantly decreased by 23.53% (*P* < 0.01) at 1 year, but the difference at 5 years was not significant. Oppositely, the duration of and disability induced by dyskinesias increased by 52.63% and 59.65%, respectively, at 5 years, and continuously got worse.

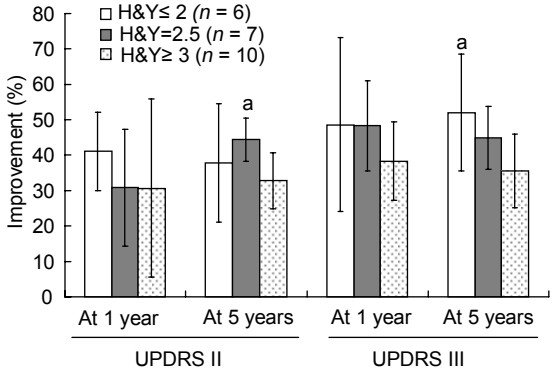

Figure 2 Improvements in Unified Parkinson's Disease Rating Scale (UPDRS) II & III scores at 1 and 5 years analyzed by Hoehn and Yahr (H&Y) stages.

In summary, lower H&Y stage was associated with greater improvements in UPDRS II and III scores ([a]*P* < 0.05, *vs.* H&Y stage ≥ 3).

A least significant difference *t*-test analysis of stages ≤ 2, 2.5 and 3 showed that the improvement of UPDRS III was significantly different between stage ≤ 2 and stage ≥ 3 at 5 years (*P* = 0.014). Data are expressed as mean ± SD.

A significant difference in the degree of improvement in UPDRS II scores was also found between patients in stage 2.5 and those in stage ≥ 3 (*P* = 0.036) at 5 years postoperation. The improvement calculation was compared with baseline [$(1-\frac{UPDRS}{baseline})$×100%].

Table 4 Unified Parkinson's Disease Rating Scale (UPDRS) IV scores with medication-on & stimulation-on after unilateral deep brain stimulation of the subthalamic nucleus in 23 patients and comparisons with baseline

Item	Score range	Preoperation	1 yr
UPDRS-IV dyskinesias duration			
UPDRS-IV dyskinesias disability	0–4	0.57±0.84	0.91±0.85
UPDRS-IV off duration	0–4	1.70±0.63	1.30±0.47

Item	5 yr	*P* value	
		At 1-yr *vs.* preoperation	At 5-yr *vs.* preoperation
UPDRS-IV dyskinesias duration	0.91±0.79	0.057	0.031
UPDRS-IV dyskinesias disability	1.04±0.98	0.043	0.013
UPDRS-IV off duration	1.87±0.63	0.026	0.315

The preoperative UPDRS IV score was assessed with medication-on. At 1 and 5 yr of follow-up, UPDRS IV score was assessed with both medication-on and stimulation-on. yr: Year.

Stimulation parameters were kept stable with no severe adverse events postoperatively

Postoperative magnetic resonance imaging verified that

all electrodes were properly located in the STN in all patients. The mean stimulation voltage increased from 2.64 ± 0.36 V at 1 year to 2.73 ± 0.36 V at 5 years. There were no severe or permanent adverse events related to the surgery procedure and short-term stimulation. Six patients had deeper voices compared with before surgery at 5 years, but not at 1 year postoperation. The deeper voices were not affected by turning the stimulation on or off. Therefore, this may be part of the natural process of PD. No patients became lethargic after the procedure (lethargy is a common side effect of the bilateral procedure). A few patients felt numbness and dizziness during parameter programming, but these symptoms disappeared immediately after reprogramming.

DISCUSSION

An increasing number of clinical reports addressing unilateral STN DBS have shown inspiring results based on short term follow-ups[10-14]; however, to our knowledge, there have been few reports with a systemic 5-year follow-up. This study showed that the efficacy of unilateral STN DBS could be maintained for at least 5 years after operation, which is a similar result to that obtained with bilateral STN DBS as reported by previous studies[15-22].

Our data showed that unilateral STN DBS was not as effective as the bilateral procedure in terms of the total UPDRS scores in a long-term follow-up. Previous studies have shown that the improvements in UPDRS II scores obtained with bilateral STN DBS ranged from 38% to 41.4% and that improvements in UPDRS III scores ranged from 29.3% to 55% with a long-time follow-up[15-22]. These improvements are smaller than those reported by most other authors. However, almost all contralateral motor scores were lower than ipsilateral ones with stimulation on. All contralateral motor symptoms were well controlled, providing considerable benefit to the patients. The ipsilateral motor symptoms were slightly improved compared with the synchronous stimulation-off state, but the improvement was no more than 20%. Similar results were reported by studies for short-term follow-up[12-13, 23-26].

The axial scores were not statistically significantly improved compared with baseline, which is different from the results of other reported studies showing improvements of approximately 20% compared with baseline[12]. This difference possibly occurred because the scores in the stimulation-off state significantly increased during the 5 years as PD symptoms worsened. The mechanism underlying the improvement in axial scores shown by other studies remains unclear, but most researchers believe that the excitability of the ipsilateral premotor cortex is restored by unilateral DBS, because approximately 20% of the corticospinal tracts run ipsilaterally to the axial muscles[23, 25]. Overall, patients with serious axial symptoms, especially posture problems, may have little chance of symptom improvement following unilateral STN DBS.

The persistent efficacy of unilateral STN DBS is convincing but asymmetrical[16-17]. The next question is what kind of PD would enable good results from unilateral STN DBS. First, all patients' parkinsonian symptoms must be highly asymmetrical, but an exact definition of "highly asymmetrical PD" is still not available. Motor scores on the more and less affected sides, side differences, and H&Y stage are some factors that can be used to evaluate asymmetry. However, none of them is a predictor of long-term improvements in symptoms based on binary logistic regression analysis. Further analysis showed that lower H&Y stage may be associated with greater improvements in symptoms with longer follow-ups. H&Y stage might be a key point for predicting improvements in symptoms. The most important factor influencing the result might be sample size. Therefore, more studies are needed to identify suitable predictors.

It is also important to consider how a patient might be able to avoid a second procedure. Unfortunately no prediction factors were identified. Taba *et al* [10] showed that patients who chose a second DBS procedure had significantly higher baseline UPDRS-III motor and ipsilateral UPDRS-III scores, and a significantly lower asymmetrical index, than those who did not. However, despite the patients involved in Han-Joon Kim's study being highly asymmetrical, all of them needed to undergo a second surgery on the opposite side within 2 years of the initial surgery[14], which indicated that asymmetry might be required but not essential. A low enough baseline and slow advancement on the less affected side are also considered to be important. In this study, there were six patients whose motor scores on the less affected side were > 19.70 (the preoperation mean score on the more affected side) at 5 years. Only one of them had a low baseline (motor score = 8), but the disease in that patient worsened rapidly (motor scores of less affected side increased by 13). The baseline scores of the others ranged from 14 to 20 and their motor scores on the less affected side increased by 6–8 during the 5-year study period, which is higher than average increase (3.33). If disease advances quickly (in our study, the mean worsened motor score among nine greatly worsened cases was 7.77 per 5 years), then the motor score on the less affected side should be lower than 11.93. Thus, patients with baseline motor scores on the less affected side of < 11 and not showing a rapid increase over the previous 3–5 years represent good

candidates for STN DBS. However, more research is required to verify this.

Unilateral STN DBS also allowed significant decreases in the doses of levodopa administered to be made. The average LEDD decreased by 33.92% at 1 year and 24.91% at 5 years. However, bilateral DBS was more effective than unilateral DBS in decreasing LEDD according to our bilateral result (decrease in LEDD by 40.36%) and other reports (decrease in LEDD by 35–63%)[15-22]. The decrease in LEDD led to the control of some levodopa-related complications such as average off-duration in the waking day, but it seemed not to be useful for alleviation of dyskinesias. The duration of and disability induced by dyskinesias continued to get worse. One obvious reason for this was that the LEDD did not decrease as much following unilateral DBS as it did following bilateral DBS and sometimes it was not easy to set a drug therapeutic regimen to balance the positive effects of the drugs and the dyskinesias on both sides. However, there may be some other reasons for this worsening of dyskinesias, and more research is required.

This was a single centre study involving 31 patients, but only 23 completed the final follow-up. The sample size is not powerful enough to demonstrate the long-term efficacy of unilateral STN DBS or its limitations. Risk factors for a second operation could not be identified owing to the small sample size. More patients should be involved with fewer patients being lost to follow-up in subsequent studies. Examiner bias may also influence the accuracy and reliability of the findings in this study, but is difficult to exclude. Only daily life quality and motor symptom improvements are presented, and the lack of neuropsychological evaluation means a comprehensive assessment of unilateral STN DBS was not possible.

Unilateral STN DBS is an effective treatment for asymmetrical PD patients. It can significantly improve contralateral motor symptoms and quality of daily life as well as remarkably decrease the dose of levodopa required. Asymmetrical PD patients with a low H&Y stage whose less affected side symptoms not showing a rapid worsening over a long period may be considered good candidates for unilateral STN DBS. Meanwhile, patients with serious axial symptoms and dyskinesias should be cautiously selected for the procedure, and should be adequately informed of the risks.

SUBJECTS AND METHODS

Design

A single-blinded prospective cohort study.

Time and setting

Between January 2000 and October 2004, all involved patients received preoperational accessments and procedures in the Neurosurgery Department of Changhai Hospital of the Second Military Medical University, Chinese PLA, China. Patients were evaluated 3–5 days before the procedure and followed up for 12 and 60 months after the procedure in the same hospital.

Subjects

Patients

A total of 23 consecutive asymmetrical PD patients underwent unilateral STN DBS. All participants gave informed consent and signatures after being advised of the risks prior to the surgeries and study, according to the *Administrative Regulations on Medical Institutions*, issued by the State Council of China[27].

Inclusion criteria to receive the unilateral procedure

All patients were clinically diagnosed with primary Parkinson's disease, suffering from severe motor complications or were not satisfied with the effects of the drug treatments they had received, despite optimal adjustment of anti-parkinsonian medication[3]. All patients were levodopa responsive. Additionally, only asymmetrical patients, whose parkinsonian symptoms on the more affected side were much more severe than those on the less affected side, were enrolled.

Exclusion criteria to receive procedure

Patients with general surgical contraindications (such as infection and bleeding), dementia or major ongoing psychiatric illness, severe encephalatrophy, brain trauma or a history of neurosurgery were excluded. Also, patients were excluded if the parkinsonian symptoms on the less affected side had significantly worsened in the previous 3 years.

Methods

Neurosurgical procedure of unilateral STN DBS

Patients were fitted to a Cosman-Robert-Wells frame that was oriented parallel to the infraorbitomeatal line under local infiltrative anesthesia and then received a magnetic resonance imaging scan (1.5 Tesla; Siemens, Erlangen, Germany). The position of the target (STN) was estimated by direct visualization in magnetic resonance images.

A bone hole was drilled over the coronal suture under local anesthesia and the dura was opened adequately for direct cortical exposure. A quadripolar lead (model 3387 or 3389; Medtronic Minneapolis, MI, USA) was used to conduct the stimulation. A guide tube for the DBS lead with a blunt tip stylet was introduced into the brain parenchyma to a point 10 mm proximal to the target. Test stimulation was performed to record voltage thresholds for stimulation and adverse effects. The electrode was

anchored to a burr-hole ring by wedging it into a groove. Another plastic burr-hole cap locked them further. An internal pulse generator (IPG, Itrel II or Soletra 7426; Medtronic) was placed in the infraclavicular fossa subcutaneously under general anesthesia. Postoperative magnetic resonance imaging (1.5 Tesla; Siemens) or CT (Siemens) scans were arranged in all patients within 24 hours postoperatively to confirm the electrode locations.

UPDRS and H&Y stage were assessed before and after surgery

Patients were evaluated 3–5 days before surgery and at 12 and 60 months after surgery using the UPDRS and H&Y staging scales[28]. All assessments were performed by one neurologist who was blinded to the patients' status of stimulation and medication. Preoperative assessments were performed when the patients had taken no medication for over 12 hours (off-medication). Postoperatively, patients were evaluated in two conditions: stimulation-off (stimulation stopped for 15–20 minutes) and stimulation-on (stimulation switched on for at least 20 minutes). Both conditions were off-medication to evaluate the effect of DBS. Dyskinesias were assessed with medication-on before surgery and with medication-on and stimulation-on during follow-ups. The optimum drug therapy was managed by neurologists. The stimulation parameters were programmed by the same neurosurgeon. The LEDD was calculated as follows: 100 mg of standard levodopa = 130 mg of controlled-released levodopa = 10 mg bromocriptine = 1 mg pergolide = 1 mg lisuride = 1 mg pramipexol[15].

Statistical analysis

Data are presented as mean ± SD. Statistical analysis was performed using SPSS 13.0 software (SPSS, Chicago, IL, USA). Improvements compared with baseline were calculated using the following equation: $\left(1-\frac{postop-UPDRS}{baseline}\right)$ × 100%. Improvements compared with the synchronous stimulation-off state were calculated using the equation: $\left(1-\frac{UPDRS-on}{UPDRS-off}\right)$ × 100%. The % decrease in LEDD was calculated as follows: $\left(1-\frac{postop-LEDD}{preop-LEDD}\right)$ × 100%. The least significant difference *t*-test was used to compare UPDRS II (total scores), III (total scores and subscores), and IV (items 32, 33 and 39) scores, as well as axial subscores, at different times and in different states (preoperational baseline, stimulation-off at 1 and 5 years). UPDRS III axial subscores were calculated from items 18 (speech), 22 (neck rigidity), 27 (rising from chair), 28 (posture), 29 (gait) and 30 (posture stability). Contralateral and ipsilateral resting tremor, action tremor, rigidity and bradykinisia were calculated from items 20 (resting tremor), 21 (action tremor), 22 (rigidity) and 23–26 (bradykinisia), respectively. Side motor scores were calculated from items 20–26 (resting and action tremor, rigidity, finger taps, hand movements, rapid alternating and leg agility of each side)[28]. Binary logistic regression analysis (backwards: conditional) was performed to find prediction factors for improvement. The improvements in UPDRS II and III were set as 1 when they were > 40%, or as 0 when they were < 40%. The variables included side (left or right STN), gender, age, age of onset, PD duration, motor score on the more affected side, motor score on the less affected side, side difference, preoperational H&Y stage and LEDD. The Student's *t*-test was performed to analyze differences in improvements with different procedure sides and the least significant difference *t*-test was also used to compare differences in improvements between different H&Y stages. The threshold for significance was a *P* value of 0.05. All *P*-values reported are two-sided.

Acknowledgments: We are grateful to Xiaojun Hou, Professor of Neurology, Changhai Hospital, the Second Military Medical University of Chinese PLA, for his advice on diagnosis and medication for the patients. We also wish to thank the staff of the Radiology Department, Changhai Hospital, the Second Military Medical University of Chinese PLA, for their technical support in magnetic resonance imaging and CT scanning.

Funding: The study was supported by the foundation of Science and Technology Commission of Shanghai Municipality, No. 101195400.

Author contributions: Jinchuan Liang collected, integrated and statistically analyzed the data, and wrote the first draft of the manuscript. Xiaowu Hu conceived and designed this study, and modified the manuscript. Xiaowu Hu, Xiaoping Zhou, Yiqun Cao, Laixing Wang, and Xiufeng Jiang were in charge of the neurosurgery procedure and provided basic clinical data. Aiguo Jin contributed to MRI and CT scanning and image analyses. Jianmin Liu contributed to the statistical analyses and the conduct of this study.

Conflicts of interest: None declared.

Ethical approval: All research activities were approved by the Changhai Hospital Ethics Committee at the Second Military Medical University of Chinese PLA, China. The final decision to undergo the unilateral procedure depended on the patient's will as well as the clinical judgment of the surgical group.

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(Edited by Zhang JG, Zhang GM/Yang Y/Song LP)