Journal of Clinical Neuroscience 21 (2014) 107–110

Contents lists available at SciVerse ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

Parkin mutation and deep brain stimulation outcome

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ARTICLE INFO

Article history:
Received 12 October 2012
Accepted 9 March 2013

Keywords:
Deep brain stimulation
Neurophysiology
Parkin
Parkinson's disease
Subthalamic nucleus

ABSTRACT

Patients with *parkin* mutations are expected to be good candidates for deep brain stimulation (DBS) because of an excellent levodopa response and frequent occurrence of levodopa-induced dyskinesia. However, there are insufficient data on surgical outcome in patients with *parkin* mutations. This study aimed to compare the outcome of subthalamic nucleus DBS in patients with early-onset Parkinson's disease with and without *parkin* mutations. Fourteen patients with early-onset Parkinson's disease who underwent bilateral subthalamic nucleus DBS surgery were screened for *parkin* mutations and assessed for surgical outcomes at baseline and 2–5 years after surgery. Three patients had homozygote/compound heterozygote mutations; two had single heterozygote mutations; and nine had no mutations. Patients with homozygote/compound heterozygote mutations were younger at disease onset and had longer disease duration than patients without a *parkin* mutation. Postoperatively, there were no significant differences in improvement on the Unified Parkinson's Disease Rating Scale part II, III, and IV, or the reduction of levodopa equivalent daily doses between patients with and without *parkin* mutations. The therapeutic effect of DBS did not differ between patients with and without *parkin* mutations.

1. Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an efficacious symptomatic treatment for Parkinson's disease (PD).[1,2] Following STN-DBS, cardinal motor symptoms of the disease are likely to be significantly improved, and the clinical benefits induced by STN stimulation are similar to those observed with levodopa treatment.[1,3]

Patients with *parkin* mutations are known to have slower disease progression and a better response to levodopa at low doses than patients with idiopathic PD,[4–6] and may exhibit frequent and early occurrence of levodopa-induced dyskinesia.[4,5] Thus, they are likely to be very good candidates for DBS. To our knowledge, however, there are insufficient data on surgical outcome in patients with *parkin* mutations. To predict surgical outcome in a patient with a *parkin* mutation, which is helpful for making a decision for surgery, we compared the outcome of STN-DBS in early-onset PD (EOPD) patients with and without *parkin* mutations.

2. Patients and methods

2.1. Patients and data collection

Among 122 patients with PD who underwent bilateral STN-DBS surgery at the Movement Disorders Center, Seoul National University Hospital (SNUH), Seoul, Korea, between 2005 and 2009, 18 were patients with EOPD, defined as an age at onset (AAO) of ⩽40 years. Four patients out of 18 were excluded as follows: one patient who initially underwent unilateral surgery; one patient who did not have long term follow-up data; one patient in whom the position of one electrode was out of the STN; and one patient for whom genetic test results were not available. Thus, the remaining 14 EOPD patients were retrospectively enrolled for this study.

Clinical diagnoses of PD were established according to the United Kingdom Parkinson Disease Society Brain Bank criteria, with the exception of the positive family history criterion.[7] Neurosurgical procedures were performed as previously described.[8] All patients were examined by movement disorder specialists, who were blinded to' genetic status, at the SNUH. A SNUH Institutional Review Board approved this study, and written informed consent to approve the genetic study was obtained from each patient.

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http://dx.doi.org/10.1016/j.jocn.2013.03.026

2.2. Clinical assessment

Patients were evaluated preoperatively and also 2 to 5 years postoperatively by using the Unified Parkinson's Disease Rating Scale (UPDRS), the Hoehn and Yahr (HY) stage,[9] and the Schwab and England scale of global activities of daily living (ADL).[10] In the baseline evaluation, UPDRS part III (mUPDRS) and HY stage were assessed in the practically defined off-medication state[11] and during the best on-medication state after the administration of a usual morning dose of dopaminergic treatment. Postoperatively, patients were assessed during stimulation. If a patient did not take any dopaminergic medication postoperatively, we assumed that the mUPDRS in the off-medication and on-medication were equal.

Levodopa equivalent daily doses (LEDD) were determined as follows:[8] 100 mg of standard levodopa = 140 mg of controlled-release levodopa = 10 mg of bromocriptine = 1 mg of pergolide = 1 mg of pramipexole = 4 mg of ropinirole. Good-awake time was calculated as [awake time − (dyskinesia duration + off duration)]. Subjective health status was evaluated with the Short Form 36 (SF-36) Health Survey.

2.3. Molecular genetic analysis

Venous blood samples were drawn and genomic DNA was extracted using standard techniques. Gene studies of *parkin*, *PINK-1*, *DJ-1*, *SNCA*, *LRRK2 G2019S*, *SCA2*, and *SCA17* mutations were conducted as described elsewhere.[12–15] *Parkin* mutations were identified by both sequence analysis and gene dosage analysis (multiplex ligation-dependent probe amplification P051/P052 kit [MRC-Holland, Amsterdam, The Netherlands]). Detailed methods have been previously described.[16]

2.4. Statistical analysis

The primary outcome measures were comparison of improvement in the mUPDRS scores and reduction of LEDD at 2–5 years after surgery between patients with *parkin* mutations (PARKIN+ group) and those without *parkin* mutations (PARKIN− group). The secondary outcome measures were comparison of the changes in UPDRS part II and part IV (items 32, 33, and 39), and total scores (0–176), subscores of mUPDRS, HY stage, ADL and the SF-36 questionnaire after surgery between PARKIN+ and PARKIN− groups. Subscores of mUPDRS were tremor (items 20 and 21), rigidity (item 22), akinesia (items 23–26), orofacial (items 18 and 19), and postural instability/gait dysfunction (PIGD) (items 27–30).[17]

Differences in the categorical variables between PARKIN+ and PARKIN− groups were analyzed using Fisher's exact test. Mann–Whitney U tests were used to analyze differences between groups. Compared with baseline data, the effects of DBS on the mUPDRS scores and the change in LEDD after surgery were analyzed with the Wilcoxon signed-rank test or Student's *t*-test. Data are presented as mean ± standard deviation values. The level of statistical significance was set at $p < 0.05$. All of the data were analyzed using the Statistical Package for the Social Sciences software (version 17.0, SPSS, Chicago, IL, USA).

3. Results

3.1. Baseline demographic and clinical characteristics

Among the 14 EOPD patients, five *parkin* mutation carriers were identified comprising three homozygote/compound heterozygote patients and two single heterozygote patients. The two single heterozygotes were excluded from the analysis of outcome measures. None of the patients had *PINK1*, *DJ-1*, *SNCA*, *LRRK2 G2019S*, *SCA2*, or *SCA17* mutations.

The mean age of the 12 remaining EOPD patients at the time of STN-DBS was 51.5 ± 8.5 years. Their mean AAO was 31.3 ± 7.6 years and the mean disease duration at operation was 18.7 ± 7.3 years. As shown in Table 1, the PARKIN+ group had a significantly younger AAO and longer disease duration than the PARKIN− group.

There were no differences between the two groups in terms of overall parkinsonian symptoms and ADL score before surgery (Table 2). All of the patients had advanced PD with motor complications. The baseline LEDD was lower in the PARKIN+ group than in the PARKIN− group; however, the difference was not significant.

3.2. Primary outcomes

Mean follow-up duration after DBS surgery was similar in the PARKIN+ and PARKIN− groups (45.7 ± 19.1 months and 50.0 ± 12.0 months, respectively; $p = 0.600$). Only the last available follow-up data were analyzed in our comparison of the outcomes of STN-DBS between the two groups.

In the 12 EOPD patients, the mean improvement in mUPDRS score was 50.2 ± 24.1%. The improvement in mUPDRS score in the PARKIN− group was greater than in the PARKIN+ group, although the difference between the two groups was not significant (Table 2). The LEDD decreased from the baseline by approximately 75% at the last follow-up in both the PARKIN+ and PARKIN− groups. Four out of the 12 patients did not take any dopaminergic medication at the last follow-up (one in the PARKIN+ group and three in the PARKIN− group).

3.3. Secondary outcomes

In the 12 EOPD patients, the mean improvement of UPDRS part II and total scores were 27.6 ± 62.7% and 42.0 ± 31.2%, respectively. Dyskinesia duration and disability were reduced by 84.5 ± 48.3% and 90.2 ± 23.8%, respectively.

There were no significant differences in the changes in UPDRS total scores, HY stage, and ADL score after surgery between the PARKIN+ and PARKIN− groups (Table 2). The off-medication PIGD subscore was significantly lower in the PARKIN− group than in the PARKIN+ group after surgery (Supp. Table 1; $p = 0.036$), however, the other mUPDRS subscores were similar between the two groups. With regard to the UPDRS part II scores, the improvement was greater in the PARKIN+ group than in the PARKIN− group, however, the difference was not significant.

Compared with the baseline scores, in the off-medication/on-stimulation state, there were significant improvements in tremor, rigidity, akinesia, and PIGD scores, mUPDRS, and UPDRS total scores, HY stage, and ADL scores in the PARKIN− group ($p < 0.05$, Wilcoxon signed-rank test). The changes in these factors were not significant in PARKIN+ group, with the exception of ADL score

Table 1
Baseline characteristics of the PARKIN+ and PARKIN− groups

	PARKIN+	PARKIN−	*p* value[†]
Number of patients	3	9	
Male:Female	1:2	5:4	
Age at operation (years)	49.7 ± 16.2	52.1 ± 5.8	0.864
Age at onset (years)	21.7 ± 8.5	34.6 ± 3.9	0.018
Disease duration at operation (years)	28.3 ± 7.6	15.4 ± 3.4	0.009
Family history, n (%)	2 (66.7)	1 (11.1)	0.127

Data are shown as mean ± standard deviation unless otherwise indicated.
PARKIN+ = *parkin* mutation-positive, PARKIN− = *parkin* mutation-negative.
[†] Mann-Whitney U test.