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High frequency stimulation of the subthalamic nucleus is efficacious in *Parkin* disease

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■ **Abstract** High frequency stimulation (HFS) of the subthalamic nucleus (STN) is an efficacious symptomatic treatment for Parkinson's disease. We have analysed the genetic status of a series of consecutive parkinsonian patients implanted for STN HFS and compared the outcome of five carrying mutations in the *parkin* gene with that of the non-*parkin* group. All patients obtained sustained control of PD symptoms and achieved functional improvement; in the *parkin* group the UPDRS motor score improved by 56.4 %, the lev-

odopa equivalent daily dosage was reduced by 75.5 %. Postoperative medications were reduced more in *parkin* than in non-*parkin* patients. We confirm that the current inclusion criteria for STN HFS do not exclude patients carrying mutations in the *parkin* gene; their clinical outcome is comparable to that of the non-*parkin* group.

■ **Key words** neurostimulation · deep brain stimulation · Parkinson's disease · surgery · subthalamic stimulation · PARK2 · parkin disease

Abbreviations

HFS	High-frequency stimulation
PD	Parkinson's disease
LEDD	Levodopa equivalent daily dose
STN	Subthalamic nucleus
UPDRS	Unified Parkinson's disease rating scale

Introduction

Parkin disease (*Park2*; OMIM 602544) is an autosomal recessive juvenile parkinsonism associated with several point mutations or rearrangements affecting the 12 coding exons of the PARK2 gene. Homo- or heterozygous nonsense, missense and frame shift mutations, or exon duplications or deletions of this gene have been described in families or in sporadic cases. The phenotypic spectrum of the disease is variable, including early-onset (usually in the third decade in European patients),

prominent and precocious dystonic symptoms, slow, relatively benign progression, sustained response to levodopa and to dopamine agonists. However, early complications of dopaminergic treatment, such as motor fluctuations or dyskinesias are frequent in *parkin*-positive patients [1, 2].

Until the *parkin*-specific genetic test became available in clinical practice, juvenile-onset Parkinson's disease (PD) was considered a variant of idiopathic PD with earlier occurrence and higher incidence of levodopa-related motor complications [3]. High frequency stimulation (HFS) of the subthalamic nucleus (STN) has been used for several years to treat PD patients with motor complications: it reduces medication requirements and provides a satisfactory control of motor fluctuations and dyskinesias [4]. Since STN HFS seems to be more effective in juvenile-onset PD [5], we have retrospectively analysed the genetic status of a series of consecutive parkinsonian patients implanted over the last seven years and report on the outcome of five with abnormalities in the *parkin* gene.

Patients and methods

Thirty-six patients, with sporadic parkinsonian features matching the clinical diagnostic criteria for PD [6], were treated by STN HFS. Eligibility for STN implant was based on previously reported criteria [7]. In brief, quadripolar leads were implanted bilaterally in the STN under stereotactic guidance: in patients 1 and 5 stereotactic placement was performed by using a ventriculographic reconstruction of the target [7]; in patients 2, 3 and 4 a virtual ventriculography was obtained by high resolution brain image fusion technique [8]. No patient had autonomic, cognitive or psychiatric disturbances at the time of enrolment in the study. Each patient was examined by brain MRI and was assessed using a preoperative and postoperative standard protocol [7]. The location of stimulating leads was verified postoperatively, by means of CT and MRI. The levodopa-equivalent daily dosage (LEDD) and the energy delivered by STN-HFS were calculated as previously described [7].

Park2 mutations were identified on DNA obtained from peripheral lymphocytes, after obtaining informed consent. SSCP analysis of the 12 exons was followed by nucleotide sequencing whenever an SSCP-band shift was observed. To detect alterations of gene dosage (deletions and duplications) a quantitative RT-PCR assay was performed [9].

Statistical analysis was carried out using Wilcoxon's matched pairs test for nonparametric variables; the limit for statistical significance was $p < 0.05$. The comparison of *parkin* with non-*parkin* patients was carried out using repeated measures of variance considering DBS-implant as within-subjects factor and *parkin* status as between-subjects factor.

Results

Five patients were found positive for mutations or rearrangements in the *parkin* gene. A total of four mutations were found, two of which were novel (G828A and G535A) and not present in 100 control alleles. Patient 1 was a compound heterozygote for a missense mutation (G828A) and a duplication of exon 1, patients 2–5 were heterozygous for mutations or duplications in the *parkin* gene (Table 1). Patient 4 had a 47-year-old sister affected by juvenile-onset PD; the other patients were sporadic. All patients had a sustained response to levodopa. The comparison of *parkin* patients with the non-*parkin* group revealed no differences in age at disease onset, at first levodopa prescription and at time of implant. In addition, there were no between-group differences in the location of stimulating leads.

All the *parkin* patients had dyskinesias, consisting in peak-dose limb dystonia (especially the lower limbs), end-of-dose limb dystonia, followed by severe peak-dose generalized choreic dyskinesias. Particularly patients 1, 3, 4 and 5 had severe peak-dose dystonia of the neck and trunk. By comparison, about 40% of non-*parkin* patients had severe disabling dyskinesias.

All the *parkin* patients improved significantly following STN HFS (Table 2). Wearing-off, off periods and dyskinesias disappeared in all patients. Neuropsychological testing revealed no cognitive variations. A comparison with the non-*parkin* group revealed no differences in UPDRS motor scores and in preoperative

Table 1 Demographic and clinical features of patients with *parkin* disease, compared to non-*parkin* patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Parkin patients (average $\pm$ SD)	Non-parkin patients (average $\pm$ SD)	p values
Gender	M	M	F	M	M	4M/1F	17M/14F	
Observed parkin gene mutations	G828A and Dupl ex1	DelAG 202–203	C1101T	G535A	Dupl ex1			
Age of disease onset (years)	45	32	41	32	27	35.4 $\pm$ 7.4	43.5 $\pm$ 6.2	0.158 ^a
Disease duration at first levodopa prescription (years)	2	4	1	1	5	2.6 $\pm$ 1.8	3.7 $\pm$ 2.4	0.225 ^a
Disease duration at onset of fluctuations (years)	5	9	18	10	10	10.0 $\pm$ 5.3	8.4 $\pm$ 4.3	0.134 ^a
Motor improvement with acute levodopa challenge (before implant, variation of UPDRS motor score)	–62.3 %	–81.4 %	–29.8 %	–60 %	–59 %	–60.6 %	–59.0 %	
Age at implant (years)	53	42	63	48	42	49.6 $\pm$ 8.8	57.4 $\pm$ 6.8	0.079 ^a
Disease duration at implant (years)	7	10	22	16	15	14.0 $\pm$ 5.8	13.9 $\pm$ 5.5	0.071 ^a
Follow-up (months)	18	12	12	12	36	21.6 $\pm$ 13.1	25.6 $\pm$ 13.8	0.145 ^a
Medications prescribed at implant (daily dosage)	levodopa 500 mg, trixyphenidyl 4 mg	levodopa 1150 mg, pramipexole 1.925 mg	levodopa 700 mg, entacapone 600 mg, cabergoline 2 mg	levodopa 1000 mg, cabergoline 2 mg	levodopa 1200 mg, pergolide 6 mg			
Medications prescribed at last FU (daily dosage)	cabergoline 4 mg	cabergoline 4 mg	cabergoline 2.5 mg, levodopa 200 mg	cabergoline 2.5 mg, levodopa 200 mg	levodopa 150 mg			

FU follow up; SD standard deviation; UPDRS Unified Parkinson's Disease Rating Scale. Statistical significance: ^a not significantly different from parkin patients

Table 2 Clinical outcome of STN HFS. Values with stimulation are compared with baseline values

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Parkin patients (average $\pm$ SD)		Non-parkin patients (average $\pm$ SD)	
	Before	Last visit	Before	Last visit	Before	Last visit	Before	Last visit	Before	Last visit	Before	Last visit	Before	Last visit
UPDRS motor score	61	35	70	17	47	37	50	17	61	20	57.3 $\pm$ 9.3	25.2 $\pm$ 10.0 ^a	59.7 $\pm$ 11.3 ^b	29.0 $\pm$ 12.3 ^c
Without medication	23	30	13	17	33	30	20	15	25	17	22.8 $\pm$ 7.3	21.8 $\pm$ 7.5 ^d	24.5 $\pm$ 14.2 ^e	21.1 $\pm$ 10.4 ^f
With medication		-43 %		-76 %		-21 %		-66 %		-67 %		-56 %		-51 %
Variation without medication														
LEDD	500	280	1285	280	1230	375	1150	374	1800	150	1193 $\pm$ 463.8	291.8 $\pm$ 92.3 ^g	1306 $\pm$ 692.0 ^h	591.2 $\pm$ 431.6 ⁱ
Variation		-44 %		-78 %		-70 %		-68 %		-92 %		-76 %		-55 %
Energy delivered (μ W)		2.31		0.35		0.87		0.34		1.45	0.0	0.97 $\pm$ 0.92	0.0	1.58 $\pm$ 0.85 ^j

LEDD, Levodopa-equivalent daily dosage; SD, Standard deviation

Statistical significance: ^a Significantly different from pre-implant value ($p = 0.043$); ^b Not significantly different from parkin patients ($p = 0.500$); ^c Significantly different from pre-implant value ($p = 0.001$), not significantly different from parkin patients ($p = 0.500$); ^d Not significantly different from pre-implant value ($p = 0.685$); ^e Not significantly different from parkin patients ($p = 0.892$); ^f Not significantly different from pre-implant value ($p = 0.231$), not significantly different from parkin patients ($p = 0.685$); ^g Significantly different from pre-implant value ($p = 0.043$); ^h Not significantly different from parkin patients ($p = 0.628$); ⁱ Significantly different from pre-implant value ($p = 0.043$), not significantly different from parkin patients ($p = 0.687$); ^j Significantly different from pre-implant value ($p = 0.043$), not significantly different from parkin patients ($p = 0.128$)

LEDD. Postoperative LEDD was reduced by a higher degree in *parkin* patients than in the non-*parkin* group and less energy was required; however, the latter difference was not significant.

No group-related difference in adverse events was observed. Worsening of parkinsonian hypophonia was observed in patient 4 as well as in 12 non-*parkin* patients. Stimulation-dependent paresthesias and stimulation-dependent ballistic-choreic dyskinesias occurred in patients 1 and 4 as well as in some non-*parkin* patients. Patient 5 developed mania and hypersexuality following the implant (reported as patient 2 [10]), and very similar features also occurred in a non-*parkin* patient (reported as patient 1).

Discussion

The present observation provides evidence that patients with *parkin* disease can benefit from STN HFS. *Parkin* patients had clinical features indistinguishable from those of non-*parkin* patients matching the UK Brain Bank criteria for PD [6] and the inclusion criteria for STN implant [7]. In particular, acute challenge with levodopa produced identical motor improvement in the *parkin* and non-*parkin* groups (Table 1). The clinical outcome was comparable with that of non-*parkin* PD patients and the stereotactic coordinates of the active contacts did not differ between groups. It is remarkable that the average dose of dopaminergic medication prescribed to the *parkin* group following the implant was approximately half of that prescribed to the non-*parkin* group, but this difference did not reach statistical significance (Table 2). The observation of a similar outcome following STN HFS indicates that similar pathophysiological basal ganglia abnormalities occur in *parkin* and non-*parkin* patients.

Parkin patients had typical clinical features, combining parkinsonian signs, dystonia and sustained responsiveness to levodopa [1, 2]; however they could not be distinguished from non-*parkin* patients based on pure clinical criteria. Only patient 4 had familial occurrence of PD; this is not surprising, because the disease is transmitted as a rare autosomal recessive trait [2]. Only patient 1 carried abnormalities in both alleles; the possibility of heterozygous patients with evidence of mutations or rearrangements detected in only one *parkin* allele has been repeatedly reported, suggesting that abnormalities in the intronic regions or in control regions of the gene may be present in the second, apparently unaffected, allele [1, 11]. In keeping with this, there were no differences in the clinical features or outcome following STN HFS between patient 1 and the remaining 4 patients. Approximately 40 % of *parkin* mutations affect a single allele in subjects that are clinically undistinguishable from homozygous or compound heterozygous *parkin*-positive patients [1, 11].

It has already been reported that the efficacy of STN HFS is directly related to the quality of preoperative response to levodopa [5]. This feature is observed also in *parkin* patients, whose response to an acute preoperative levodopa challenge predicts the postoperative outcome. Side-effects and adverse events observed in *parkin* patients, including mood disorders, were also comparable with those observed in other series of STN-implanted patients [4]. As a rule, they were minor and not disabling.

In summary, it is notable that current inclusion crite-

ria for STN surgery also apply to patients with *parkin* disease, who have a comparable outcome with lesser medication requirement than non-*parkin* patients. This further suggests that genetic testing for *parkin* disease is not a mandatory requirement for the selection of candidates to STN implants.

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