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### Stereotactic pallidotomy in Parkinson's disease

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# Chapter 2

## Unilateral pallidotomy in advanced Parkinson's disease: a retrospective study of 26 patients

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## Summary

**Objective** To evaluate the effects of unilateral pallidotomy in patients with Parkinson's disease.

**Patients and methods** Twenty-six patients with Parkinson's disease and disabling dyskinesias, painful and/or disabling dystonia, and/or pain as part of Parkinson's disease despite optimal pharmacotherapy underwent a unilateral pallidotomy. For assessment the unified Parkinson's disease rating scale (UPDRS) activities of daily living and motor section, Hoehn and Yahr staging, the Schwab and England scale, a dyskinesia rating scale, and timed tests were used. Assessment was performed in defined 'off' and 'on', and on average 2 months before and 7.5 months after the unilateral pallidotomy. Adverse effects were classified as transient or permanent, and as major or minor.

**Results** In the off phase the median UPDRS activities of daily living score improved from 26.5 to 20.5 (23 percent) and the median UPDRS motor score improved from 47.5 to 33.0 (31 percent). In the on phase, the dyskinesia rating scale score was reduced from median 2 to 1 ( $p < 0.001$ ), and the total UPDRS activities of daily living and motor scores remained unchanged. Thirteen patients had transient adverse effects, three patients had permanent and two patients had a combination of transient and permanent adverse effects. The transient adverse effects in two patients were classified as major.

**Conclusions** Stereotactic unilateral pallidotomy can improve symptoms and disability in the off phase. In the on phase, dyskinesias disappeared at the side contralateral to the procedure. Permanent minor complications of pallidotomy occurred in 19 percent of the patients.

## Introduction

With the publication by Laitinen et al.<sup>1</sup> in 1992 stereotactic pallidotomy was reintroduced as a symptomatic treatment for Parkinson's disease. Cohort studies indicate that pallidotomy improves parkinsonism in the 'off' phase and reduces dyskinesias in the 'on' phase.<sup>2-11</sup> In most of the studies evaluating patients in standardised off and on phases, microelectrode recording followed by stimulation was used to outline the globus pallidus before lesioning.<sup>2,3,5-11</sup> There are a few studies published with patient assessment in standardised on and off phases and macroelectrode stimulation only to verify the target structure.<sup>4,12</sup> Therefore, we report the results of our first 26 consecutive patients with Parkinson's disease and a unilateral pallidotomy without microelectrode recording assessed in standardised off and on phases.

## Patients and methods

**Patients** Twenty-six patients with Parkinson's disease underwent a unilateral pallidotomy (table 1). Indications for pallidotomy were severe and disabling dyskinesias, painful and disabling dystonia and/or pain as part of Parkinson's disease despite optimal pharmacological treatment. Exclusion criteria were contraindications for stereotactic neurosurgery (physical condition making surgery hazardous, severe hypertension, blood coagulation disorder, severe dysphagia, and dysphasia) and moderate to severe cognitive dysfunction, as shown with a mini mental state examination<sup>13</sup> of 24 or less. The seventh

**Table 1.** Baseline characteristics of the 26 patients

Characteristic	Value
Sex (male/female)	14/12
Age in yrs	55.8 (40-74)
Duration of disease in yrs	15.3 (4-29)
Age at onset of PD in yrs	40.4 (29-53)
Side of surgery (right/left)	13/13
Hoehn and Yahr stage	
Off-period median (range)	4 (1-5)
On-period median (range)	2.5 (1-5)
Daily preoperative medication dosages	
L-dopa	
No of patients	26
Dose in mg*	836 (157-5000)
Pergolide	
No of patients	15
Dose in mg	2.1 (0.15-8.0)
Lisuride in two patients	0.4 and 0.8 mg
Apomorphine sc continuously in three patients	50, 70 and 70 mg

Data are mean (range) unless otherwise stated; PD=Parkinson's disease; sc=subcutaneous;

\*without peripheral decarboxylase inhibitor

patient operated had Parkinson's disease for 23 years and was wheelchair bound in her best on phase. Despite an improvement of hand functioning and disappearance of dyskinesias, she remained wheelchair-bound and very disabled. Since then, we exclude patients for operation with Hoehn and Yahr stage<sup>14</sup> 5 in their best on phase. Seventeen patients had young-onset Parkinson's disease.<sup>15</sup> Three patients had mainly unilateral symptoms. The 23 other patients had a level of disability that interfered seriously with self-care and activities of daily living.

**Assessment** The scales used were the second and third part of the unified Parkinson's disease rating scale (UPDRS; activities of daily living and motor examination sections),<sup>16</sup> Hoehn and Yahr staging, the Schwab and England scale,<sup>16</sup> and the dyskinesia rating scale proposed by Goetz et al.<sup>17,18</sup> The body weight of the patients was also noted.

The following timed tests, recommended by the core assessment program for intracerebral transplantations (CAPIT) committee, were part of the assessment protocol for the last 20 patients: the pronation-supination test, the tapping test and the stand-walk-sit test.<sup>18</sup>

All clinical rating scales were performed in defined off and on phases, except the dyskinesia rating scale, which was rated in the on phase only. The off phase was defined as the condition of the patient after withholding antiparkinson medication for 12 h and being awake for at least 1 h. The on phase was the condition 1 h after taking the usual first morning dose. Assessment was performed at a median of 1 week (range 1 day - 45 weeks) before (baseline) and 5 months after the pallidotomy (range 1 week - 24 months, 10 patients < 3 months).

Preoperatively, patient assessment was performed by JDS (neurologist, one patient), PRS (neurosurgery resident, three patients) and RdB (neurology resident, 22 patients). Postoperatively, all patients were assessed by RdB, who was not blinded for the treatment.

For analysing the effects of unilateral pallidotomy several items of the UPDRS, for each side of the body, were combined as follows: tremor = arm and leg rest tremor and arm action tremor (scores no 20 + 21); akinesia = finger taps, hand movements, rapid alternating movements of the hand, and leg agility (scores no 23 + 24 + 25 + 26); rigidity = arm and leg rigidity (scores no 22); postural instability/gait disorder (PIGD) = posture, gait, and postural stability (scores no 28 + 29 + 30). We analysed the effect on speech (scores no 5 + 18) and sensory disorders related to parkinsonism (score no 17).

For analysing possible changes in pharmacological treatment, we pooled different drugs together in levodopa-equivalent units (LEU) according to the following conversion formula: 100 LEU = 100 mg levodopa, given with a peripheral decarboxylase inhibitor = 133 mg levodopa (plus peripheral decarboxylase inhibitor) in controlled-release tablets = 1 mg pergolide mesylate.

**Surgical technique** Patients were started on a short schedule of low-dose corticosteroids (phase-out from 10 mg per day in 5 days) the night before surgery to reduce oedema around the lesion. Antiparkinson drugs were withheld on the day of surgery until the end of the procedure. The Leksell stereotactic frame (Elekta Instruments, Stockholm, Sweden) was applied under local anaesthesia. A burr hole with a diameter of 10 mm was made 2-3 cm lateral from the midline just anterior to the coronal suture. For the ventriculography, 10 ml iohexol (240 mg I/ml) was injected into the lateral ventricle. The target coordinates for the posteroventral globus pallidus at the border of the medial and lateral segments were 2 mm anterior to the midcommissural point, 5 mm below the intercommissural line and 22 mm lateral to the midline of the third ventricle. Microelectrode recording and microelectrode stimulation were not performed. In the trajectory towards the calculated target point, electrical monopolar test stimulation was carried out, using an electrode with a  $2.1 \times 4.0$  mm bare tip, in 2 mm steps starting 8 mm above the target in the first 20 patients and 6 mm above the target in the last six patients. The stimulus parameters used were: pulse width 0.1 msec (rectangular monophasic), frequency 2 Hz (low) and 130 Hz (high), and voltage up to 8 V. Low-frequency stimulation was used to determine proximity of the internal capsule. If myoclonus were not observed using low-frequency stimulation with a threshold up to 4 V, the distance to the capsule was considered safe for lesioning. High-frequency stimulation was used for testing the effects on tremor, rigidity and hypokinesia, and for side effects, such as speech disorders, parasthesias, abnormal eye movements, and visual stimulation responses. Hypokinesia was tested by pronation-supination movements of the hand, finger dexterity, opening and closing of the hand, and leg movements. If the threshold for myoclonus and side effects was higher than 4 V, radio-frequency thermolesions were produced at 80°C for 60 s directly after stimulation at each 2-mm step. If the patient had any visual stimulation responses with high-frequency stimulation, no lesion would be placed because this could endanger the optic tract.

**Adverse effects** Transient (< 3 months) or permanent (> 3 months) adverse effects were classified according to the following properties. Adverse effects that interfered with the patient's daily routine were considered major adverse effects. If they caused minimal or no interference with the patient's daily routine, they were labelled minor. Observations concerning medication and adverse effects are reported with a follow-up ranging from 3 months to 2 years.

**Statistical analysis** All data were analysed with Wilcoxon signed-ranks test statistics for the ordinal scales. The timed tests and weight were analysed with a *t* test. A difference with  $p < 0.01$  was considered significant. Timed tests of a patient were excluded for statistical analysis if the patient had not accomplished both the preoperative and postoperative series.

## Results

**The off state** Patients improved 31 percent on the total UPDRS motor section and 23 percent on the activities of daily living section score (table 2). Patients also improved significantly on the Schwab and England scale and in Hoehn and Yahr stage.

All UPDRS item composite scores improved significantly on the side contralateral to the side of surgery. The PIGD composite score improved 38 percent. There was a slight worsening of speech and a slight improvement of sensory complaints. Both were not statistically significant (table 3).

The timed tests were part of the assessment protocol in 20 patients. Four patients could not complete the preoperative contralateral pronation-supination test, but three of them completed the test postoperatively. The contralateral pronation-supination test of the other 16 patients improved 18 percent (table 4). One patient could not accomplish the pre- and postoperative tapping tests, both contra- and ipsilateral. The mean duration of the tapping tests of the other 19 patients improved contra- and ipsilateral with 42 and 25 percent, respectively (table 4). Only 13 patients could accomplish the stand-walk-sit tests pre- and postoperatively, the mean postoperative time being 3.8 s shorter compared with the preoperative time. The reduction was not significant. Two patients could only complete the postoperative stand-walk-sit test (table 4).

**The on state** The UPDRS motor section, the UPDRS activities of daily living section, the UPDRS symptom composite scores, and the Schwab and England scale did not change significantly (table 2 and 3). The dyskinesia rating scale score was reduced from median 2 to 1 (table 5).

The timed tests did not change significantly. One patient was unable to complete the postoperative ipsilateral pronation-supination test, although she could complete it preoperatively. Two patients could not accomplish the preoperative

**Table 2.** Results of assessments before and after unilateral pallidotomy in 26 patients

	Before median (range)	After median (range)	Change median (95% CI)
<b>Off phase</b>			
UPDRS motor	47.5 (13-74)	33.0 (5-74)	14.0 (8.5 to 19.5)†
UPDRS ADL	26.5 (10-47)	20.5 (5-40)	5.5 (3.0 to 8.5)†
Schwab and England scale	50 (10-90)	65 (20-90)	15 (10 to 20)†
Hoehn and Yahr stage	4 (1-5)	3 (1-5)	0.5 (0.25 to 1)*
<b>On phase</b>			
UPDRS motor	17.5 (1-53)	15.0 (1-63)	1.0 (-4.0 to 5.0)
UPDRS ADL	12.0 (2-37)	11.0 (1-34)	1.0 (-1.5 to 3.0)
Schwab and England scale	80 (30-100)	85 (20-100)	5 (0 to 10)
Hoehn and Yahr stage	2.5 (1-5)	2 (1-5)	0.25 (0 to 0.5)*

ADL=activities of daily living; \*  $p < 0.01$ ; †  $p < 0.001$ .

**Table 3.** Effects of unilateral pallidotomy as measured with combined items of the UPDRS on main parkinsonian symptoms in off and on phases in 26 patients

		Before median (range)	After median (range)	Change median (95% CI)
<b>Off phase</b>				
Akinesia	ipsilateral	-8.0 (0-15)	7.0 (0-14)	0.5 (-5.0 to 2.0)
	contralateral	10.5 (0-16)	6.5 (2-13)	3.5 (1.5 to 5.0)†
Rigidity	ipsilateral	3.0 (0-7)	2.0 (0-8)	1.0 (0.0 to 1.5)
	contralateral	3.5 (1-8)	2.0 (0-6)	1.5 (1.0 to 2.5)†
Tremor	ipsilateral	2.0 (0-11)	1.0 (0-10)	1.0 (0.5 to 1.5)
	contralateral	3.5 (0-10)	0.5 (0-10)	2.5 (1.5 to 3.5)*
PIGD		6.5 (1-12)	4.0 (0-12)	2.5 (1.5 to 3.5)†
Speech		3.0 (0-7)	4.0 (1-8)	-1.0 (-1.5 to 0)
Sensory Complaints		2.0 (0-4)	1.0 (0-4)	0.5 (0.0 to 1.0)
<b>On phase</b>				
Akinesia	ipsilateral	3.5 (0-9)	4.0 (0-13)	0.0 (-1.5 to 0.5)
	contralateral	5.0 (0-13)	4.5 (0-11)	0.5 (-1.0 to 1.5)
Rigidity	ipsilateral	1.0 (0-6)	1.0 (0-7)	0.0 (-0.5 to 0.5)
	contralateral	1.0 (0-5)	1.0 (0-5)	0.0 (-0.5 to 0.5)
Tremor	ipsilateral	0.0 (0-4)	0.0 (0-1)	0.0 (0.0 to 0.0)
	contralateral	0.0 (0-9)	0.0 (0-7)	0.0 (0.0 to 0.5)
PIGD		2.0 (0-12)	1.0 (0-11)	1.0 (0.5 to 1.5)
Speech		2.0 (0-6)	3.0 (0-8)	-1.0 (-2.0 to 0.0)
Sensory Complaints		0.0 (0-3)	0.5 (0-3)	0.0 (-0.5 to 0.5)

PIGD=postural instability/gait disturbances; \*  $p < 0.01$ ; †  $p < 0.001$ .

contralateral pronation-supination test, which they completed postoperatively. Three patients could not complete the preoperative stand-walk-sit test, of which one could complete it postoperatively. One patient could complete the test preoperatively, but was unable to perform it postoperatively (table 4). The mean body weight increased from 67.4 kg to 71.8 kg ( $p < 0.01$ ).

**Lesion location** In 23 patients only one track was used. In two patients a second track was used 2 mm more lateral because low-frequency stimulation produced myoclonus at low thresholds in the first track. In one patient three test tracks were made. A low threshold for myoclonus prompted a position 2 mm more lateral, after which three lesions were made. Because there was no improvement of parkinsonism, a third track was tested with stimulation, again 2 mm more lateral. As improvement of symptoms was observed, in this track an additional 4 lesions were made. The mean number of thermolesions produced was 4.5 (range 3-7) per patient. Magnetic resonance image scanning was done in 16 patients more than 3 months after the pallidotomy. In three patients computed tomography scans were performed 3 months postoperatively. Lesions were situated in the posterior and ventral part of the globus pallidus pars externa (GPe) and interna (GPi) in 15 patients. Two of these patients had an extension of the lesion at the dorsal side, which probably represented small infarctions. In

**Table 4.** Results of timed tests in 20 patients, expressed in seconds

		n*	Before pallidotomy mean (SD)	After pallidotomy mean (SD)	Change (95% CI)
<b>Off phase</b>					
Pronation-supination test	ipsilateral	17	16.6 (3.9)	17.3 (5.8)	-0.6 (-4.4 to 3.1)
	contralateral	16	18.6 (5.5)	15.3 (3.4)	3.3 (0.6 to 5.9)
Tapping test	ipsilateral	19	12.2 (5.0)	9.2 (3.5)	3.0 (1.4 to 4.6)†
	contralateral	19	15.0 (6.7)	8.7 (3.6)	6.3 (3.1 to 9.5)†
Stand-walk-sit test		13	16.5 (6.3)	12.6 (5.7)	3.8 (-1.7 to 7.8)
<b>On phase</b>					
Pronation-supination test	ipsilateral	19	14.9 (3.0)	15.3 (6.6)	-0.4 (-2.9 to 2.2)
	contralateral	18	16.1 (4.9)	14.3 (3.1)	1.9 (-0.1 to 3.8)
Tapping test	ipsilateral	20	8.8 (2.9)	8.5 (4.4)	0.4 (-1.3 to 2.1)
	contralateral	20	10.1 (4.6)	8.4 (5.0)	1.6 (-0.9 to 4.3)
Stand-walk-sit test		16	12.9 (4.0)	12.0 (2.6)	0.9 (-0.3 to 2.1)

\* Number of patients who accomplished preoperative and postoperative timed tests; †  $p < 0.01$ .

three patients the lesions extended in the posterior part of the GPe up to the boundary with the putamen. One patient had a lesion more anteriorly in the GPe close to the putamen. The effectiveness of the pallidotomy in the latter four patients was the same as in the patients in which the lesions included the internal and external segments of the globus pallidus.

**Medication** The medication was changed as little as possible for the first 3 postoperative months. The pooled antiparkinson medication was slightly reduced from 841 LEU (SD 643) at baseline to 816 LEU (373) at follow-up assessment, which was not statistically significant. Lisuride and apomorphine medication were not changed postoperatively.

**Adverse effects** Thirteen patients (50 percent) had transient adverse effects, three (12 percent) had permanent and two (8 percent) a combination of transient and permanent adverse effects (table 6).

Major transient adverse effects were seen in two patients who were disoriented after the pallidotomy which interfered with their daily routine directly. In one case this lasted for several weeks. In the other case there was major disorientation for several days after which a permanent reduction in motivation remained.

All other transient side effects were classified as minor: facial paresis (seven), dysarthria (six), mild short-lasting disorientation (one), and feelings of depression (one). Five patients had bouts of hiccups, which started on the day of surgery or the following day and lasted for 2 or 3 days. Two patients noticed mild chorea of the contralateral arm and leg lasting for several hours directly following pallidotomy. We did not classify this as an adverse effect because it is associated with a favourable surgical outcome.<sup>7</sup> In both patients the lesions were situated

**Table 5.** Effects of unilateral pallidotomy on dyskinesias in the on state as measured with the dyskinesia rating scale proposed by Goetz et al.<sup>17</sup> in 25 patients

Value	Before (number of patients)	After (number of patients)
0	3	10
1	9	10
2	6	3
3	6	2
4	1	-

Median difference 1.0; 95% confidence interval 0.5-1.0;  $p < 0.001$ .

**Table 6.** Adverse effects of unilateral pallidotomy in 26 patients

	Number of patients
<b>Transient (n=13)</b>	
Facial paresis	4
Dysarthria	2
Disorientation	2
Facial paresis + hiccups	2
Dysarthria + hiccups	2
Facial paresis + dysarthria + depressed	1
<b>Permanent (n=3)</b>	
Facial paresis	1
Facial paresis + emotionally less stable	1
Dysarthria + reduced motivation	1
<b>Transient and Permanent (n=2)</b>	
Dysarthria (transient) + disorientation (transient)+ reduced motivation (permanent)	1
Hiccups (transient) + impaired concentration (permanent)	1

in the posteroventral globus pallidus including the medial and lateral segments. Permanent complications were mild facial paresis (two), dysarthria (one), and higher cerebral dysfunction (four) such as reduced motivation, emotional instability and impaired concentration. Formal neuropsychological evaluation, however, was at that time not yet part of the research protocol.

## Discussion

A shortcoming of the present study is the range in follow-up assessment. In the study by Lang et al. effects on off state subscores for tremor, rigidity, and bradykinesia were sustained for 2 years; the improvements of gait disorders and postural stability however, were not.<sup>5</sup> The total UPDRS scores were fairly stable for 2 years. In other studies with follow-up ranging from 1-4 years and multiple assessments, postoperative parkinsonism and contralateral dyskinesias were fairly stable.<sup>3,4,19</sup> The progression of symptoms therefore probably is small compared to the initial effects of pallidotomy.

**Parkinsonism and dyskinesias** In the off state, the improvement on the total UPDRS motor score consists of reduced tremor, akinesia and rigidity scores contralateral to the side of the pallidotomy. The UPDRS activities of daily living score and the Schwab and England scale improved in the off state, indicating that the changes in impairment improved the level of disability. In the on state, dyskinesias were strongly reduced after unilateral pallidotomy, in contrast to the UPDRS motor score, the UPDRS activities of daily living score and the Schwab and England scale, which did not improve. These results are consistent with other reports concerning unilateral pallidotomy and alternative methods for target localisation like magnetic resonance imaging, computed tomography, and microelectrode recording.<sup>2,3,5,6,9,10</sup>

The UPDRS motor and activities of daily living scores in the off phase postoperatively remained worse than the on phase scores pre- and postoperatively. The on state scores, except for dyskinesias, were not changed by pallidotomy. This indicates that improvements in the off phase after pallidotomy do not exceed improvements from antiparkinson drugs and that it is important to assess the patient's best level of functioning while evaluating eligibility for unilateral pallidotomy because the patient will probably not improve beyond this level.

We observed an improvement of PIGD signs indicating that impairment of balance and walking can improve by unilateral pallidotomy. This is supported by the reduction in time for the stand-walk-sit test, which was not significant, probably as a result of the small number of patients. Other groups also found a reduction in PIGD signs or a decreased performance time for the stand-walk-sit test.<sup>2,4,8,9</sup> In the study by Lang et al.<sup>5</sup> this effect was not permanent.

Patients with pain due to parkinsonism often reported relief of pain on the contralateral body side.

**Timed tests** The tapping test improved contra- and ipsilaterally in the off phase. The other tests did not change significantly, but some patients were not capable of accomplishing all the timed tests recommended by the CAPIT committee.<sup>18</sup> This is in agreement with other reports and it shows how demanding the tests are for these patients.<sup>9,10</sup> Some patients could postoperatively complete a test which they could not preoperatively. This indicates an improvement, but we excluded the tests for statistical analysis if a patient could not accomplish both series. In the tests proposed by the CAPIT committee, the score would be infinite if a patient can not perform a certain manoeuvre necessary for a timed test. This score is not feasible for analysis. If, however, the time to perform the manoeuvres would be fixed, for example, 30 s, and the score of the test would be the number of completed movements, for example, number of movements between two points 30 cm apart, the score would be zero, which could be used for analysis.

**Adverse effects** Two patients had transient disorientation as a major adverse effect and five patients had minor permanent adverse effects. Thirty percent of the patients had no adverse effects. The frequency of adverse effects in the present study is in agreement with other studies.<sup>5,9,10</sup> In most of these studies microelectrode recording is used for target localisation. The most serious complications of stereotactic neurosurgery are intracerebral haemorrhage or infarction, which can be fatal and can occur even in experienced hands.<sup>20</sup>

**Lesion location** Laitinen reported to produce lesions at the border of the GPi and GPe, including parts of both structures.<sup>1</sup> Later he moved the target 2 mm more lateral.<sup>21</sup> Others reported their lesions were in the GPi.<sup>22</sup> At least four patients in our group had a lesion restricted to the GPe. The effects seen in these patients were the same compared to patients with lesions including both GPe and GPi. According to the pathophysiological model of Parkinson's disease proposed by DeLong<sup>23</sup> in which the output of the medial segment of the globus pallidus is increased, one would expect that a lesion in the GPi would alleviate parkinsonism more effectively compared to a lesion in the GPe.<sup>24</sup>

**Surgical technique** We do not use microelectrode recording during the procedure. The necessity of this technique for adequate, safe procedures is still controversial. Microelectrode recordings are technically demanding for the clinical setting and lengthen the procedure considerably. Samuel et al.<sup>9</sup> and Shannon et al.<sup>10</sup> discuss the possible relationship between the number of electrode tracks and the intracerebral haemorrhages. They do not find a relationship in their studies but the groups are probably too small to exclude it.

**Conclusion** Severe dyskinesias, dystonia, or pain accompanying Parkinson's disease not improving with optimal pharmacotherapy can improve with unilateral pallidotomy, especially if the symptoms are asymmetrical. Our results are in agreement with other reports concerning unilateral pallidotomy and alternative methods for target localisation like magnetic resonance imaging, computed tomography and microelectrode recording. Gait and postural instability problems in the off phase can improve. Adverse effects can be severe, and this has to be taken into account while selecting patients for pallidotomy.

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