

LONG-TERM FOLLOW-UP OF UNILATERAL PALLIDOTOMY IN ADVANCED PARKINSON'S DISEASE

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ABSTRACT

Background Although the short-term benefits of posteroventral pallidotomy for patients with advanced Parkinson's disease have been well documented, little is known about the long-term outcome of the procedure.

Methods We conducted a long-term follow-up study of a cohort of 40 patients who had undergone unilateral posteroventral medial pallidotomy between 1993 and 1996. Twenty patients were not evaluated because they had undergone a second surgical procedure (11 patients) or had died (2) or because they had dementia or another debilitating illness (4), lived too far away (1), or had been lost to follow-up (2). We conducted serial postoperative assessments of parkinsonism in the remaining 20 patients while they were taking medications ("on" period) and after overnight withdrawal of the drugs ("off" period). The mean follow-up time was 52 months (range, 41 to 64).

Results The combined off-period score for activities of daily living and motor function on the Unified Parkinson's Disease Rating Scale was 18.0 percent better at the last evaluation than at base line (95 percent confidence interval, 4.9 to 31.0 percent; $P=0.01$). Significant improvements were also evident in the off-period scores for contralateral tremor (65.4 percent improvement, $P=0.007$), rigidity (43.2 percent, $P=0.03$), and bradykinesia (18.2 percent, $P=0.04$) and in the on-period score for contralateral dyskinesia (70.6 percent, $P<0.001$). Changes in medication did not contribute to the sustained improvement. The 20 patients who could not be included in the long-term analysis had similar base-line characteristics but a worse response to surgery at six months.

Conclusions In the group of patients with advanced Parkinson's disease who could be enrolled in our long-term follow-up study of unilateral posteroventral medial pallidotomy (20 patients from the original cohort of 40), significant early improvements in off-period contralateral signs of parkinsonism were sustained for up to 5½ years. There was a sustained significant improvement in on-period contralateral dyskinesia but not in other on-period signs of parkinsonism. (N Engl J Med 2000;342:1708-14.)

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BECAUSE of the limited efficacy of medical treatment for Parkinson's disease and because of advances in technology and in our understanding of the function of the basal ganglia,¹ certain patients with advanced Parkinson's disease are being treated surgically. Since the re-introduction of posteroventral medial pallidotomy,² numerous centers have reported significant benefits of this procedure.³⁻⁹ Most studies have demonstrated postoperative improvements in motor function and activities of daily living, with consistent improvements in contralateral bradykinesia, tremor, and rigidity after an overnight withdrawal of medications ("off" period) and with particular improvements in contralateral dyskinesias while patients are taking medications ("on" period). The degree and duration of ipsilateral improvements vary among studies, and the results with respect to on-period signs of parkinsonism other than dyskinesia are contradictory.

Although data from a large number of studies support the efficacy of pallidotomy in the treatment of advanced Parkinson's disease, most of these data are based on assessments performed within the first year after surgery. We know of only three studies with longer follow-up periods; in two of these studies, patients were followed for up to two years,^{4,9} and in one, 10 patients were evaluated more than two years after surgery.⁵ Thus, little is known about the long-term outcome of a procedure that is widely viewed as an important adjunctive therapy in the advanced stages of Parkinson's disease and that is the most common surgical treatment for the disorder. We report long-term follow-up data on 20 of 40 patients who underwent unilateral posteroventral medial pallidotomy for medically intractable Parkinson's disease.⁴

METHODS

Patients

The patients in our follow-up study were part of a cohort of 40 patients who underwent posteroventral medial pallidotomy between June 1993 and January 1996.⁴ This study was approved by the Toronto Hospital Committee for Research on Human Subjects, and the patients gave written informed consent for surgery and for ongoing follow-up evaluations.

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TABLE 1. BASE-LINE CHARACTERISTICS OF THE 20 PATIENTS.*

CHARACTERISTIC	VALUE
Sex (no. of patients)	
Male	15
Female	5
Age (yr)	
Mean	57.1±7.1
Range	45–69
Duration of disease (yr)	
Mean	11.9±3.7
Range	5–21
Hoehn and Yahr stage†	
On period	
Median	2.5
Range	1.5–3
Off period	
Median	3.25
Range	2.5–4.5
Schwab and England ADL score (%)‡	
On period	
Mean	81.3
Range	50–100
Off period	
Mean	44.5
Range	10–70

*Plus-minus values are means ±SD.

†The Hoehn and Yahr stage of parkinsonism is based on a scale ranging from 0 to 5, with a lower stage indicating better function.

‡The Schwab and England score for activities of daily living (ADL) is based on a scale ranging from 0 to 100, with a higher score indicating better function.

Of the 40 patients, 20 were not included in the current study. Eleven of these 20 patients subsequently underwent a second surgical procedure. One patient underwent an ipsilateral pallidotomy six months after the first procedure because the benefit of the original procedure was not sustained; the second procedure resulted in long-lasting improvement. The other 10 patients underwent a contralateral procedure to treat disability stemming largely from the unoperated side. Three of the 10 patients underwent contralateral pallidotomy 8, 16, and 18 months after the first procedure, with improvement in all 3 patients, particularly with respect to disabling dyskinesias. However, debilitating cognitive and behavioral complications developed in two of the three patients,¹⁰ and this outcome prompted us to make a smaller lesion on the second side when subsequently using this approach. Two patients with pronounced tremor on the ipsilateral side underwent successful contralateral deep-brain stimulation of the thalamus 10 and 32 months after the pallidotomy. Five patients with other disabling parkinsonian features on the unoperated side underwent deep-brain stimulation of the contralateral globus pallidus 12 to 40 months (mean, 21) after the pallidotomy, with further benefit.¹¹ Of the other nine patients who were not evaluated, two died, four had dementia or other debilitating conditions, one lived too far away, and two were lost to follow-up. The remaining 20 patients were all assessed and are the primary focus of this analysis.

The base-line characteristics of the patients are shown in Table 1. All patients underwent microelectrode-guided posteroventral medial pallidotomy as described in detail elsewhere.^{4,12,13} The antiparkinsonian medications that the patients received were changed during the years after surgery, and some patients received newer agents such as pramipexole and tolcapone. The doses of antiparkinsonian medications before surgery and at the last evaluation are

TABLE 2. ANTIPARKINSONIAN MEDICATIONS AT BASE LINE AND AT THE LAST EVALUATION.

MEDICATION	BASE LINE	LAST EVALUATION
Levodopa plus PDCI*		
No. of patients	20	20
Dose (mg)		
Mean	1110	1148
Range	400–1900	400–2050
Bromocriptine		
No. of patients	8	5
Dose (mg)		
Mean	20.6	28.0
Range	5.0–40.0	17.5–50.0
Pergolide		
No. of patients	7	11
Dose (mg)		
Mean	3.1	4.4
Range	1.0–6.0	0.5–14.0
Pramipexole		
No. of patients	0	1
Dose (mg)	—	2.25
Tolcapone		
No. of patients	0	3
Dose (mg)		
Mean	—	333
Range	—	300–400
Total levodopa-equivalent dose†		
No. of patients	20	20
Dose (mg)		
Mean	1300±564	1554±580
Range	200–2350	600–2250

*PDCI denotes peripheral decarboxylase inhibitor.

†There was no significant difference between the mean total levodopa-equivalent dose at base line and at the last evaluation ($P=0.17$ by Student's *t*-test).

shown in Table 2. The total levodopa-equivalent dose was calculated as the sum of the dose of regular levodopa-carbidopa (or levodopa-benserazide), plus 0.75 times the dose of controlled-release levodopa-carbidopa, plus 10 times the dose of bromocriptine, plus 100 times the dose of pergolide, plus 100 times the dose of pramipexole.¹⁴ For patients who were receiving tolcapone, the sum of the dose of regular levodopa and 0.75 times the dose of controlled-release levodopa was multiplied by a factor of 1.33.

Evaluations

Patients were evaluated as described previously,¹² according to a modified protocol of the Core Assessment Program for Intracerebral Transplantations,¹⁵ which incorporates components of the Unified Parkinson's Disease Rating Scale (UPDRS) that measure motor function (part III) and activities of daily living (part II), as well as the evaluation of dyskinesia.¹⁶ Separate scores for axial and hemibody dyskinesia were recorded. For patients who had been given new antiparkinsonian drugs or substantially increased doses of drugs since the base-line assessment, the new agents or additional doses were withdrawn 36 to 48 hours before the off-period assessment, in order to approximate base-line conditions as closely as possible. All the assessments were performed by a single investigator, who had also evaluated each patient before surgery and at each of the initial postoperative visits. All 20 patients were evaluated six months after surgery, 19 were evaluated at one year, and 17 at two years. The mean follow-up period was 52 months (range, 41 to 64).

Outcome Measures

As in our earlier study,⁴ the primary measure of efficacy was the overall off-period score on the UPDRS, defined as the sum of the

scores for activities of daily living and motor function. This combined score was considered to reflect the overall severity of functional impairment due to Parkinson's disease. The Schwab and England scale for evaluating activities of daily living (part VI of the UPDRS) was also used.

Secondary measures of efficacy included aspects of motor function that had shown sustained improvement in our earlier study: the off-period scores on the UPDRS for contralateral bradykinesia, tremor, and rigidity¹² and the on-period score for contralateral dyskinesia.¹⁶

Statistical Analysis

We performed pairwise comparisons of the base-line (preoperative) scores and the scores at the last evaluation with the use of the Wilcoxon signed-rank test for each variable. The mean total daily levodopa-equivalent doses were compared with the use of Student's t-test. For significant differences between base-line and follow-up values, the percent change in the mean value and the 95 percent confidence interval were calculated. For variables that still showed a significant improvement at the last evaluation, analysis of variance with repeated measures was used to determine whether these variables changed with time. The follow-up interval (six months, one year, two years, or the interval between surgery and the most recent evaluation) was the repeated measure.

In an attempt to identify clinical variables that were predictive of a good long-term outcome, we calculated nonparametric Spearman correlations. For the purpose of the correlational analyses, overall improvement after surgery was defined as the percent

change in the overall off-period UPDRS score (the primary outcome measure) between base line and the final assessment. Similarly, the response to surgery at six months was defined as the percent change in the off-period UPDRS score between base line and the assessment at six months. Additional components of the UPDRS that were analyzed included the preoperative response to levodopa, calculated as the difference between the total off-period and on-period motor scores, and the hemibody scores for motor function (tremor, rigidity, and bradykinesia; i.e., UPDRS items 20 through 26). To assess the generalizability of the long-term data, we used the Mann-Whitney U test to compare the 20 patients in the current study with the 20 patients in the original cohort who could not be included in this study. All reported P values are two-sided.

RESULTS

There were no significant differences in the mean total levodopa-equivalent doses of medications between base line and the most recent follow-up visit (P=0.17) (Table 2). The means (±SD) for the overall off-period UPDRS score, the component activities of daily living and motor scores, and the scores on the various subscores for motor function are shown in Table 3. The P values are for the pairwise comparison of scores at base line and at the last evaluation.

TABLE 3. MEAN OFF-PERIOD AND ON-PERIOD SCORES AT BASE LINE, SIX MONTHS, AND THE LAST EVALUATION.*

MEASURE	SCORE RANGE	BASE LINE	SIX MONTHS	LAST EVALUATION	P VALUE†
Off period					
Overall UPDRS score	0-160	66.2±14.5	41.1±16.5	56.1±18.3	0.02
Motor	0-108	41.7±12.3	25.7±11.1	33.8±12.2	0.01
ADL	0-52	24.5±5.2	15.5±7.0	22.1±7.7	0.23
Schwab and England ADL score	0-100	44.5±16.4	68.2±16.5	53.5±19.5	0.07
Contralateral motor scores					
Bradykinesia	0-16	9.0±2.6	4.8±2.4	7.4±3.0	0.04
Tremor	0-12	2.6±2.3	0.7±1.1	0.9±1.2	0.007
Rigidity	0-8	3.4±2.3	1.3±1.1	1.9±1.5	0.03
Ipsilateral motor scores					
Bradykinesia	0-16	6.7±2.9	4.9±2.9	5.7±3.6	0.3
Tremor	0-12	1.9±2.2	1.3±1.9	1.2±1.6	0.15
Rigidity	0-8	2.8±1.8	2.4±1.6	2.1±1.8	0.16
Axial motor scores					
Gait disorder	0-4	2.2±0.8	1.6±0.9	2.2±1.1	0.98
Postural instability	0-4	2.0±1.0	1.3±1.1	2.3±1.2	0.2
Freezing	0-4	2.3±1.1	1.3±0.9	2.4±1.1	0.98
Postural instability and gait disorder‡	0-20	10.0±3.8	6.4±3.4	11.0±4.9	0.43
On period					
Overall UPDRS score	0-160	23.4±8.9	19.8±10.9	29.0±12.5	0.04
Motor	0-108	15.0±7.5	13.8±8.2	17.9±8.6	0.12
ADL	0-52	8.5±4.1	6.2±4.0	11.1±5.2	0.06
Schwab and England ADL score	0-100	81.3±10.7	87.2±7.8	80.8±13.4	0.75
Contralateral dyskinesia score	0-4	2.2±0.8	0.4±0.7	0.7±1.0	<0.001
Ipsilateral dyskinesia score	0-4	1.6±0.9	1.1±0.8	1.2±0.7	0.08

*Plus-minus values are means ±SD. Lower scores indicate better function for all items except the Schwab and England activities of daily living (ADL) scores. Scores are described in detail elsewhere.³ UPDRS denotes Unified Parkinson's Disease Rating Scale.

†P values (determined with the use of the Wilcoxon signed-rank test) are for pairwise comparisons between the base-line scores and the scores of the last evaluation.

‡The scores for postural instability and gait disorder represent a composite of five items, as described in a previous report.⁴

Primary Outcome Measure

The mean overall off-period UPDRS score in the 20 patients was significantly better during long-term follow-up than at base line ($P=0.02$) (Fig. 1A). Although the change remained significant throughout the follow-up period, there was a trend toward loss of improvement, with an improvement of 37.4 percent at six months (95 percent confidence interval, 27.7 to 47.1 percent) and 18.0 percent at the final evaluation (95 percent confidence interval, 4.9 to 31.0 percent). Analysis of variance with repeated measures for scores at six months and at the final evaluation showed a significant effect of time on the scores ($P=0.001$), confirming a deterioration in the scores during the follow-up period.

There was an 18.2 percent improvement from base line in the off-period motor score during long-term follow-up (95 percent confidence interval, 4.9 to 31.4 percent; $P=0.01$). However, the postoperative scores deteriorated significantly over time ($P=0.003$ by analysis of variance with repeated measures). In addition, the improvement at six months in the off-period score for activities of daily living was not sustained, with the mean score approaching the base-line value over the follow-up period and no longer significantly different at the last evaluation (Fig. 1A). Similarly, the off-period score on the Schwab and England scale of activities of daily living was not significantly better at the final assessment than at base line ($P=0.07$).

Secondary Outcome Measures

The significant early improvements in the off-period scores for contralateral bradykinesia, tremor, and rigidity, noted in our previous reports,^{4,12} were maintained during long-term follow-up (Fig. 1B). The score for tremor improved by 65.4 percent (95 percent confidence interval, 22.4 to 108.4 percent; $P=0.007$), and the score for rigidity improved by 43.2 percent (95 percent confidence interval, 9.0 to 77.3 percent; $P=0.03$). The early amelioration of tremor and rigidity was sustained throughout the follow-up period; analysis of variance with repeated measures showed no significant effect of time on the postoperative scores. Although the improvement in the score for bradykinesia was sustained at the final assessment ($P=0.04$), analysis of variance showed that the score worsened over time ($P=0.006$).

There was sustained, significant improvement in the score for contralateral on-period dyskinesia, with a change of 70.6 percent (95 percent confidence interval, 47.2 to 94.0 percent; $P<0.001$) between base line and the last evaluation. Analysis of variance showed no significant trend toward a worsening of the score over time ($P=0.22$).

Predictors of the Long-Term Outcome

The patient's age, the duration of the disease, and the overall off-period UPDRS score at base line were not significantly correlated with the long-term out-

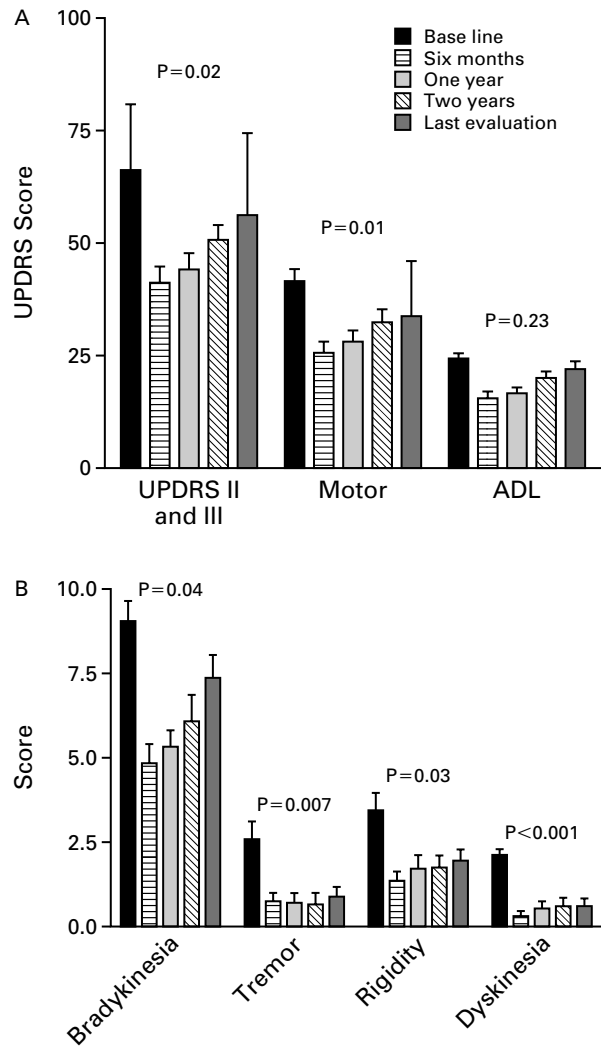


Figure 1. Mean (\pm SD) Scores for Functional Impairment (Panel A) and for Contralateral Bradykinesia, Tremor, and Rigidity (Panel B) before Surgery and during Long-Term Follow-up.

Panel A shows the off-period scores for part III (motor component) and part II (activities of daily living [ADL]) of the Unified Parkinson's Disease Rating Scale (UPDRS). Panel B shows the off-period scores for contralateral bradykinesia, tremor, and rigidity and the on-period scores for contralateral dyskinesia. P values are for comparisons of scores before surgery and at the last evaluation. Lower scores indicate better function.

come of surgery. The percent improvement in the overall off-period UPDRS score at six months was significantly correlated with the percent improvement at the final evaluation ($P=0.01$, $r=0.55$), indicating that the early response was predictive of the long-term outcome. There was a slight but significant correlation between the degree of off-period asymmetry before surgery (the score for contralateral motor function expressed as a percentage of the total motor score) and overall long-term improvement

($P=0.05$, $r=0.45$). Patients with a higher degree of contralateral motor dysfunction had a greater long-term benefit from surgery. Preoperative responsiveness to levodopa was not predictive of the percentage improvement in the off-period UPDRS score.

Ipsilateral, Axial, and On-Period Scores

Pallidotomy had no long-term benefit with respect to ipsilateral off-period or on-period motor function, including dyskinesia (Table 3). The off-period composite score for postural instability and gait disorder and the subscores for gait disorder, postural instability, and freezing were all similar at base line and at the final evaluation. The degree of axial involvement was similar at six months and at the final evaluation. The off-period score for axial motor function (the total motor score on the UPDRS minus the sum of the ipsilateral and contralateral hemibody motor scores) was 40 ± 16 percent of the total motor score at six months and 44 ± 9 percent at the final evaluation.

The overall on-period UPDRS score deteriorated over time (from 23.4 ± 8.9 before surgery to 29.0 ± 12.5 at the final evaluation, $P=0.04$). The individual ipsilateral and contralateral on-period motor subscores did not change significantly (data not shown), except for the contralateral bradykinesia score, which was worse at the final evaluation than at base line ($P<0.001$). The on-period axial scores also tended to worsen with time (data not shown). Significant deterioration was noted in the composite score for postural instability and gait disorder ($P=0.03$), as well as in the subscores for postural instability ($P=0.04$) and freezing ($P=0.05$).

Comparison with Patients Not Included in the Long-Term Analysis

A comparison between the 20 patients enrolled in the long-term analysis and the 20 who could not be included is shown in Table 4. There were no significant differences between the two groups at base line with respect to age, the overall off-period UPDRS score, and its two component scores for activities of daily living and motor function. At six months, the overall off-period UPDRS score and the motor subscore were higher in the group of patients who were not enrolled in the long-term analysis, indicating that this group derived significantly less early benefit from surgery (overall UPDRS score, $P=0.005$; motor score, $P=0.001$). At base line, the degree of responsiveness to levodopa, off-period asymmetry (hemibody motor scores), and axial involvement were similar in the two groups and therefore did not account for the difference in the overall UPDRS and motor scores at six months.

DISCUSSION

We found that pallidotomy resulted in a significant reduction in the overall off-period UPDRS score (the

TABLE 4. CHARACTERISTICS OF THE 20 PATIENTS IN THE LONG-TERM STUDY AND THE 20 PATIENTS WHO COULD NOT BE INCLUDED, AT BASE LINE AND AT SIX MONTHS.*

CHARACTERISTIC	PATIENTS INCLUDED AT FOLLOW-UP (N=20)	PATIENTS NOT INCLUDED (N=20)	P VALUE†
At base line			
Age (yr)	57.1±7.1	60.5±9.1	0.20
Duration of disease (yr)	11.9±3.7	14.2±5.2	0.76
Responsiveness to levodopa‡	26.7±10.4	28.1±10.5	0.76
Off-period UPDRS score			
Overall	66.2±14.5	72.8±11.2	0.11
ADL	24.5±5.2	24.9±5.2	0.83
Motor	41.7±12.3	47.8±9.4	0.07
Contralateral	15.2±5.2	17.0±4.9	0.23
Ipsilateral	11.4±4.8	13.3±4.2	0.23
Axial§	15.2±6.4	17.5±4.4	0.13
At six months			
Off-period UPDRS score			
Overall	41.2±16.5	56.8±13.0¶	0.005
ADL	15.6±7	19.4±6.7	0.20
Motor	25.7±11.1	37.2±7.7	0.001

*Plus-minus values are means \pm SD. UPDRS denotes Unified Parkinson's Disease Rating Scale, and ADL activities of daily living.

†P values (determined with the use of the Mann-Whitney U test) are for comparisons between the patients included in the long-term study and the patients who could not be included.

‡Responsiveness to levodopa was defined as the difference between the overall off-period and on-period scores for motor function at base line.

§The score for axial motor function was calculated as the total motor score minus the sum of the scores for ipsilateral and contralateral motor function.

¶Two excluded patients were not evaluated at six months. One had already been scheduled to undergo a second surgical procedure, and the other lived too far away.

primary outcome measure) and the component motor score; this improvement was sustained for up to 5½ years. These scores worsened with time, perhaps reflecting a loss of benefit from the surgery or progression of the disease. However, patients' clinical status was still improved at the final assessment as compared with the base-line scores. The absence of significant increases in the off-period scores for contralateral rigidity and tremor and in the on-period score for contralateral dyskinesia suggests that the initial benefit was sustained. The score for contralateral bradykinesia, like the overall UPDRS score, deteriorated with time.

In spite of the persistent improvement in off-period motor score, the initial improvement in the level of daily functioning, as reflected by the UPDRS and Schwab and England scores for activities of daily living, was not sustained. A deterioration in the off-period ipsilateral motor scores did not account for this decline. Off-period axial scores were also not significantly worse at the final evaluation than at base line, although corresponding on-period scores did worsen significantly.

The mean period of follow-up in our study was 52 months, with a range of 41 to 64 months. All patients were evaluated by a single observer throughout this study. Despite these strengths, the study was uncontrolled and unblinded, and only 20 of the 40 patients in the original cohort could be included in the long-term analysis. Thus, our findings may represent the best possible outcomes. This potential bias, however, may have been offset by the fact that the 40 patients in the original cohort were the first patients with Parkinson's disease whom we treated with pallidotomy.

Contralateral dyskinesia and levodopa-responsive signs and symptoms have been identified as the features of parkinsonism that are most likely to improve after surgery. Our study did not find any additional base-line characteristics that were significant predictors of the long-term surgical outcome. Factors such as age, the duration of the disease, and the overall severity of functional impairment (as reflected by the off-period UPDRS score) were not correlated with the degree of improvement after surgery. This finding is disappointing because it provides no insight into the optimal selection of patients for the procedure. However, the absence of significant correlations may reflect our selection criteria, which resulted in a fairly homogeneous study group. A greater degree of variation may be necessary to identify predictive factors.¹⁷ Had we included older patients or those with poor responses to levodopa, we might have had different results.

The one factor that was slightly but significantly predictive of long-term improvement was the degree of asymmetry of motor disability. This finding supports the consistent finding that the greatest and most persistent benefit of pallidotomy is its effect on contralateral motor function.

The on-period UPDRS score, a measure of the best overall level of function, deteriorated over the period of observation, as it does over time in patients who do not undergo pallidotomy. Measures of on-period axial function, such as scores for postural instability, gait disorder, and freezing, were also significantly worse over time. The increase in the on-period score for contralateral bradykinesia is less easily explained. This finding suggests that although pallidotomy improves contralateral off-period signs of parkinsonism, the bradykinesia may become less responsive to levodopa. Altered responsiveness to levodopa after pallidotomy has been reported by other investigators.^{18,19} One hypothesis is that the location of the lesion has a role in responsiveness to levodopa after surgery.²⁰

A long-term follow-up study generally has a high attrition rate. We examined this issue by comparing the final study group with all the other patients in the original cohort. We found a selection bias in the final study group in favor of patients with a better

early outcome. This bias may limit the general applicability of our results. In this respect, as well, the location of the lesion (and its size) may have had a role. The fact that more than a quarter of the patients in the original cohort were excluded because they had undergone second procedures on the contralateral side points to the inherent limitations of a unilateral procedure in the treatment of a disease process that is invariably bilateral. "Losing" patients for this reason is inevitable in a long-term study, especially since deep-brain stimulation is now believed to be safer for bilateral procedures than lesions alone.

Bilateral deep-brain stimulation has been applied to the thalamus,²¹ globus pallidus,^{22,23} and subthalamic nucleus.^{24,25} Thalamic deep-brain stimulation is predominantly effective for the treatment of tremor and is therefore likely to have a limited role in the management of Parkinson's disease at an advanced stage, when other types of disability predominate. Deep-brain stimulation of the globus pallidus and subthalamic nucleus may result in striking improvements in off-period signs of parkinsonism as well as in on-period dyskinesia. Further studies are required to determine which site of deep-brain stimulation is most effective.²⁶ Cost and other practical considerations (including the prolonged programming time that is often required) limit the widespread use of deep-brain stimulation. For patients with severe, bilateral off-period disability, however, many groups are now using bilateral deep-brain stimulation of the globus pallidus or subthalamic nucleus. Another option is to combine unilateral pallidotomy with deep-brain stimulation on the contralateral side.¹¹

Our study confirms that the amelioration of contralateral parkinsonian symptoms and medication-related dyskinesia after pallidotomy is sustained for up to five and a half years. Improvements in ipsilateral and axial symptoms are not sustained, and many patients undergo a second, contralateral procedure. Whether an initial pallidotomy alters a patient's response to other forms of therapy, such as high-frequency stimulation of the subthalamic nucleus or transplantation of fetal mesencephalic tissue, remains to be determined. Pallidotomy is nevertheless a useful treatment in selected patients with medically intractable Parkinson's disease.

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REFERENCES

1. Lang AE, Lozano AM. Parkinson's disease. *N Engl J Med* 1998;339:1044-53, 1130-43.
2. Laitinen LV, Bergenheim AT, Hariz MI. Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease. *J Neurosurg* 1992;76:53-61.
3. Baron MS, Vitek JL, Bakay RA, et al. Treatment of advanced Parkinson's disease by posterior GPi pallidotomy: 1-year results of a pilot study. *Ann Neurol* 1996;40:355-66.

4. Lang AE, Lozano AM, Montgomery E, Duff J, Tasker R, Hutchison W. Posteroventral medial pallidotomy in advanced Parkinson's disease. *N Engl J Med* 1997;337:1036-42.
5. Fazzini E, Dogali M, Sterio D, Eidelberg D, Beric A. Stereotactic pallidotomy for Parkinson's disease: a long-term follow-up of unilateral pallidotomy. *Neurology* 1997;48:1273-7.
6. Uitti RJ, Wharen RE Jr, Turk MF, et al. Unilateral pallidotomy for Parkinson's disease: comparison of outcome in younger versus elderly patients. *Neurology* 1997;49:1072-7.
7. Shannon KM, Penn RD, Kroin JS, et al. Stereotactic pallidotomy for the treatment of Parkinson's disease: efficacy and adverse effects at 6 months in 26 patients. *Neurology* 1998;50:434-8.
8. Samuel M, Caputo E, Brooks DJ, et al. A study of medial pallidotomy for Parkinson's disease: clinical outcome, MRI location and complications. *Brain* 1998;121:59-75.
9. Samii A, Turnbull IM, Kishore A, et al. Reassessment of unilateral pallidotomy in Parkinson's disease: a 2-year follow-up study. *Brain* 1999;122:417-25.
10. Galvez-Jimenez N, Lozano AM, Duff J, Trepanier L, Saint-Cyr JA, Lang AE. Bilateral pallidotomy: pronounced amelioration of incapacitating levodopa-induced dyskinesias but accompanying cognitive decline. *Mov Disord* 1996;11:242. abstract.
11. Gálvez-Jiménez N, Lozano A, Tasker R, Duff J, Hutchison W, Lang AE. Pallidal stimulation in Parkinson's disease patients with a prior unilateral pallidotomy. *Can J Neurol Sci* 1998;25:300-5.
12. Lozano AM, Lang AE, Galvez-Jimenez N, et al. Effect of GPi pallidotomy on motor function in Parkinson's disease. *Lancet* 1995;346:1383-7. [Erratum, *Lancet* 1996;348:1108.]
13. Lozano A, Hutchison W, Kiss Z, Tasker R, Davis K, Dostrovsky J. Methods for microelectrode-guided posteroventral pallidotomy. *J Neurosurg* 1996;84:194-202.
14. Goetz CG, Blasucci L, Stebbins GT. Switching dopamine agonists in advanced Parkinson's disease: is rapid titration preferable to slow? *Neurology* 1999;52:1227-9.
15. Langston JW, Widner H, Goetz CG, et al. Core assessment program for intracerebral transplantations (CAPIT). *Mov Disord* 1992;7:2-13.
16. Goetz C, Stebbins GT, Shale HM, et al. Utility of an objective dyskinesia rating scale for Parkinson's disease: inter- and intrarater reliability assessment. *Mov Disord* 1994;9:390-4.
17. Lang AE, Montgomery E, Hutchison W, Lozano A. Attempting to predict the response to pallidotomy. *Mov Disord* 1998;13:263. abstract.
18. Krack P, Pollak P, Limousin P, Benabid AL. Levodopa-inhibiting effect of pallidal surgery. *Ann Neurol* 1997;42:129-30.
19. Verhagen L, Mouradian MM, Chase TN. Altered levodopa dose-response profile following pallidotomy. *Neurology* 1996;46:Suppl:A416-A417. abstract.
20. Gross RE, Lombardi WJ, Lang AE, et al. Relationship of lesion location to clinical outcome following microelectrode-guided pallidotomy for Parkinson's disease. *Brain* 1999;122:405-16.
21. Limousin P, Speelman JD, Gielen F, Janssens M. Multicentre European study of thalamic stimulation in parkinsonian and essential tremor. *J Neurol Neurosurg Psychiatry* 1999;66:289-96.
22. Kumar R, Lozano AM, Montgomery E, Lang AE. Pallidotomy and deep brain stimulation of the pallidum and subthalamic nucleus in advanced Parkinson's disease. *Mov Disord* 1998;13:Suppl 1:73-82.
23. Volkmann J, Sturm V, Weiss P, et al. Bilateral high-frequency stimulation of the internal globus pallidus in advanced Parkinson's disease. *Ann Neurol* 1998;44:953-61.
24. Kumar R, Lozano AM, Kim YJ, et al. Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease. *Neurology* 1998;51:850-5.
25. Limousin P, Krack P, Pollak P, et al. Electrical stimulation of the subthalamic nucleus in advanced Parkinson's disease. *N Engl J Med* 1998;339:1105-11.
26. Burchiel KJ, Anderson VC, Favre J, Hammerstad JP. Comparison of pallidal and subthalamic nucleus deep brain stimulation for advanced Parkinson's disease: results of a randomized, blinded pilot study. *Neurosurgery* 1999;45:1375-82.