

# Outcomes following staged bilateral pallidotomy in advanced Parkinson's disease

**Article abstract**—The authors assessed clinical outcome for up to one year after staged bilateral pallidotomy in 14 patients with advanced PD. One year after surgery, dyskinesias were virtually abolished and there were significant reductions in “off” time (67%) and activities of daily living “off” scores (24%), as well as nonsignificant reduction in “off” motor score (39%); “on” scores were unchanged. One patient developed a visual field deficit; two had transient confusion. Staged bilateral pallidotomy improves motor function in selected patients with advanced PD.

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Unilateral posteroventral pallidotomy (PVP) improves motor function in patients with advanced PD.<sup>1-3</sup> Transient bilateral improvement in symptoms and signs often occurs, although in the majority of cases these symptoms progress over time.

Few data are published on outcomes after bilateral pallidotomy.<sup>3-9</sup> We describe clinical outcomes in 14 patients with marked clinical progression of symptoms who, after successful unilateral PVP, underwent a staged bilateral procedure.

**Materials and methods.** *Patients.* Between February 1994 and July 1998, 82 patients with PD underwent PVP at our hospital. Patients were evaluated by at least two neurologists (T.J.C., L.A.S., and J.B.P.) and a neurosurgeon (G.R.C.). Patients were considered good candidates for PVP if they had a history compatible with a diagnosis of idiopathic PD as well as motor fluctuations and disabling dyskinesias despite optimal medical therapy. Patients who had a history suggestive of atypical parkinsonism, or those with prominent postural instability, freezing of gait, or significant cognitive impairment, were declined surgery. Despite a good functional outcome after the initial surgery, 16 of these 82 patients experienced a resurgence of disabling symptoms on the side ipsilateral to the first procedure, and they subsequently underwent a staged PVP procedure on the untreated side. Two patients did not return for follow-up, leaving 14 patients (nine men and five women) from whom follow-up data were obtained at least 6 months after the second surgery. Table 1 summarizes the patient characteristics including dopaminergic therapy dosages, expressed as levodopa equivalents to account for concurrent treatment with dopamine agonists.<sup>1</sup>

*Clinical evaluations.* For the preoperative baseline neurologic evaluations, patients were examined both in the “on” state and during the “practically defined off” state according to the Core Assessment Program for Intracerebral Transplantation (CAPIT) protocol using the

Unified PD Rating Scale (UPDRS).<sup>10</sup> Dyskinesia measures were obtained in terms of intensity and duration; the intensity of dyskinesia scores was defined according to the CAPIT protocol but with a 0- to 4-point scale (0 = none or unnoticed; 1 = noticed but not bothersome; 2 = interferes with some activities of daily living [ADL]; 3 = interferes with most ADL; 4 = incapacitating). A separate score was assigned to each limb including a score for trunk and neck (maximum score = 24). Evaluations were performed at least every 6 months until 6 months after the second procedure. Data were available for 10 patients one year after the second surgery. For logistical reasons, it was not possible to obtain “practically defined off” data for all patients at each follow-up visit; hence the “off” motor score (UPDRS, Part III, items 18 to 31) is only available for a subset of patients (nine) who were examined in the “practically defined off” state at follow-up intervals. In all cases after the first pallidotomy, attempts were made to optimize the pharmacologic regimen in an effort to avert the need for a second surgical procedure.

*Surgical procedure.* Stereotactic PVP performed at our institution has been described previously.<sup>2</sup> Target selection was achieved using MRI and CT stereotactic localization and intraoperative macroelectrode stimulation.

*Statistical analysis.* In the case of the UPDRS, scores are presented as means of each subscale. Subcomponents of the UPDRS were analyzed using formulae as previously described.<sup>1</sup> All results were analyzed using the Wilcoxon signed rank test. The significance level was set at 0.05.

**Results.** Table 2 summarizes the results of UPDRS subscales, motor fluctuations, and dyskinesia scores expressed as means, standard deviations, and degrees of significance. There was no significant change in the mean levodopa-equivalent dosage during the follow-up period. Dyskinesias were virtually abolished after the staged bilateral PVP, and this improvement was maintained through the 6-month follow-up period ( $p < 0.01$ ) and for one year in the 10 patients evaluated to that point ( $p < 0.05$ ). There was a reduction in the number of hours spent in the “off” state (67%;  $p < 0.01$  at one year). There was a corresponding increase in the percentage of the waking day spent in the “on” state, with patients spending 33% more of their day “on” than prior to the initial surgery ( $p = 0.001$ ). ADL “on” scores did not change throughout the follow-up period. ADL “off” scores were improved (30%;  $p < 0.01$ ) at 6 months after the

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**Table 1** Patient characteristics

Patient no. (sex)	Disease duration, y	L-dopa equivalent, mg	Age at first surgery, y	Interval between surgeries, mo	Hoehn & Yahr "on"/ "off" scores at baseline
1 (M)	6	765	44	7	4/4
2 (F)	10	1100	59	14	2.5/3
3 (M)	6	1500	63	14	2/4
4 (F)	18	575	69	5	2/3
5 (M)	9	2400	38	15	2/4
6 (F)	15	1225	70	14	2/4
7 (M)	13	920	53	14	2/3
8 (F)	12	1100	48	15	2/3
9 (F)	10	750	42	6	2/3
10 (M)	15	1620	47	13	2/4
11 (M)	16	850	61	9	3/4
12 (M)	6	450	70	9	2.5/4
13 (M)	16	1140	60	15	2.5/4
14 (M)	27	1790	61	6	3/4
Mean $\pm$ SD	13 $\pm$ 6	1010 $\pm$ 430	59 $\pm$ 9	12 $\pm$ 4	—
Range	6–27	350–1790	42–70	5–19	—

staged surgery, compared with baseline. The UPDRS Mentation and Behavior score was not significantly changed during the follow-up period.

The mean motor "on" scores did not change significantly compared with baseline during the follow-up period. The

mean "off" motor score 6 months after the staged PVP was 36% improved compared with the prepallidotomy state, which was maintained at one year follow-up; this improvement was not significant. Tremor was improved both at 6 months ( $p < 0.01$ ) and at one year ( $p < 0.05$ ). There were

**Table 2** Motor outcomes after staged bilateral pallidotomy

Score	1st surgery/2nd surgery				
	Baseline, n = 14	6 months, n = 14	12 months/ baseline, n = 14	18 months/6 months, n = 14	24 months/12 months, n = 10
Hours "off"	8.3 $\pm$ 3.0	4.9 $\pm$ 3.7*	5.3 $\pm$ 3.4*	3.1 $\pm$ 2.7†	2.8 $\pm$ 2.3†
% Time "on"	50 $\pm$ 19	71 $\pm$ 19*	70 $\pm$ 21*	82 $\pm$ 16†	83 $\pm$ 14*
Dyskinesia intensity	8.2 $\pm$ 3.8	4.6 $\pm$ 3.7*	6.7 $\pm$ 4.3	0.2 $\pm$ 0.4*‡	0.9 $\pm$ 1.4*‡
Dyskinesia hours	5.1 $\pm$ 3.4	2.5 $\pm$ 2.6†	3.6 $\pm$ 3.5*	0.6 $\pm$ 1.2†‡	0.3 $\pm$ 0.5*
UPDRS "mentation"	2.6 $\pm$ 2.0	2.7 $\pm$ 1.9	3.2 $\pm$ 1.7	3.5 $\pm$ 1.4	3.3 $\pm$ 1.9
UPDRS ADL "on"	8.0 $\pm$ 5.1	8.7 $\pm$ 4.6	9.2 $\pm$ 4.8	10.8 $\pm$ 4.6	11.2 $\pm$ 4.2
UPDRS ADL "off"	25.4 $\pm$ 5.2	19.3 $\pm$ 4.5*	21.9 $\pm$ 7.0	18 $\pm$ 3.3†	19.1 $\pm$ 4.6†‡
UPDRS motor "on"	21 $\pm$ 15	23 $\pm$ 8	15 $\pm$ 9	21 $\pm$ 9	27 $\pm$ 13
UPDRS motor "off," n = 9	54 $\pm$ 15	27 $\pm$ 9*	40 $\pm$ 7	34 $\pm$ 13	33 $\pm$ 13
Tremor, n = 9	3.7 $\pm$ 1.7	1.7 $\pm$ 1.7*	2.2 $\pm$ 1.9	1.2 $\pm$ 0.9†	1.0 $\pm$ 1.4*
Bradykinesia, n = 9	17.7 $\pm$ 4.3	12.4 $\pm$ 4.3*	12.8 $\pm$ 3.8*	8.3 $\pm$ 5.1†	9.6 $\pm$ 4.8†
Rigidity, n = 9	10.7 $\pm$ 4.2	7.3 $\pm$ 4.2*	10.1 $\pm$ 3.6	7.1 $\pm$ 3.9*	7.2 $\pm$ 3.4*
Freezing "on"	0.5 $\pm$ 0.5	0.3 $\pm$ 0.5	0.5 $\pm$ 0.7	1.5 $\pm$ 0.9	1.7 $\pm$ 1.0
Freezing "off," n = 9	1.5 $\pm$ 0.8	0.9 $\pm$ 0.6	1.3 $\pm$ 0.8	1.7 $\pm$ 1.2	1.3 $\pm$ 0.7
PIGD "on"	1.5 $\pm$ 1.1	1.7 $\pm$ 1.2	1.5 $\pm$ 1.2	2.8 $\pm$ 2.4	3.2 $\pm$ 3.2
PIGD "off," n = 9	4.9 $\pm$ 1.5	4.2 $\pm$ 1.0	4.3 $\pm$ 1.5	5.0 $\pm$ 2.4	5.0 $\pm$ 2.7

Values expressed as mean (SD).

\*  $p < 0.05$ ; †  $p < 0.01$  compared with baseline; ‡  $p < 0.05$  compared with value before second operation.

ADL = activities of daily living; PIGD = postural instability and gait disorder; UPDRS = Unified Parkinson's Disease Rating Scale.

**Table 3** Published outcomes in patients with PD undergoing bilateral pallidotomy

Author	Patients, n	Interval between surgeries (range, mo)	Complications (no. of patients)	Comment
Laitinen, 1992 <sup>3</sup>	4	Staged (6–14)	—	No UPDRS data Transient benefit only (1 patient)
Iacono, 1995 <sup>4</sup>	68	49 contemporaneous; 19 staged (4–14)	Hemorrhages (2) Infection (1)	4.5-Month follow-up
Sutton, 1995 <sup>5</sup>	2	Staged (2–3)	Hemianopia (2) Depression (2) Increased freezing (1)	2-Month follow-up
Schuurman, 1997 <sup>6</sup>	3	Staged	Quadrantanopia (1) Transient facial paresis (1)	1 Atypical parkinsonism 1 Previous thalamotomy
Scott, 1998 <sup>7</sup>	8	Contemporaneous	Confusion (1) Hypophonia (1) Dysarthria (3) Drooling (2) Reduced verbal fluency (4)	3–4-Month follow-up
Ghika, 1999 <sup>8</sup>	4	Contemporaneous	Bulbar syndrome (1) Depression (2) Abulia (1) Compulsions (1) Apraxia of eyelid opening (1)	3–6-Month follow-up Good motor response
Favre, 2000 <sup>9</sup>	22	17 contemporaneous; 5 staged	Dysarthria >50% Dysphagia >35%	Median follow-up 7 months Good motor response

UPDRS = Unified Parkinson's Disease Rating Scale.

no significant changes found in freezing spells, either in the “on” or “off” states during the follow-up period. Similarly, postural instability and gait disorder (PIGD) showed no significant changes during the follow-up period. Two patients experienced exacerbation of preoperative gait difficulties, principally with initiation of gait. There was no group effect of staged PVP on speech, ability to handle saliva, or swallowing, with the exception that “off” swallowing improved after the first operation. There was a nonsignificant deterioration in “on” speech found at 6 months compared with the preoperative value. One patient experienced persistent worsening of preexisting dysarthria, drooling, and dysphagia. Mild hypophonia was noted in five patients postoperatively. One patient developed a permanent quadrantanopia postoperatively caused by a delayed ischemic event. Two patients developed transient postoperative confusion lasting several days after the second surgery. There were no deaths and no intracerebral hemorrhages noted on postoperative MRI scans.

**Discussion.** We present 6-month follow-up results for 14 patients who underwent staged bilateral PVP for advanced PD, with one-year follow-up data for 10 patients. The results after unilateral pallidotomy in these patients are similar to those published in recent series.<sup>1</sup>

The most dramatic result of the staged PVP was the near total abolition of levodopa-induced dyskinesias

in all patients. A similar reduction was found in measurements of motor fluctuations, although most of this benefit was obtained after the unilateral procedure. Tremor was also improved significantly. There were few bulbar complications after the staged bilateral procedure in our series. As with unilateral PVP, bilateral PVP did not improve gait or postural instability.

Published reports regarding outcomes after staged bilateral PVP are relatively few,<sup>4–9</sup> and interpretation of outcomes is hampered by inconsistencies in the use of standardized data collection and reporting. Table 3 summarizes the major published series of patients undergoing bilateral PVP since 1992. Our patients who underwent staged PVP were carefully selected on the basis of ongoing or progressive motor fluctuations and dyskinesias ipsilateral to the initial lesion; hence they are not representative of a consecutive group of patients with advanced PD. We believe that there is a role for staged bilateral PVP in such carefully selected patients. Although we found that staged bilateral PVP is associated with a higher incidence of adverse events, the widely held clinical impression that bilateral PVP leads to severe bulbar and cognitive dysfunction is not supported by our experience.

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Dedicated to the memory of the late John B. Penney, Jr., MD.

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## Mitochondrial myopathy, parkinsonism, and multiple mtDNA deletions in a Sephardic Jewish family

**Article abstract**—The authors describe a family of Sephardic Jews with progressive external ophthalmoparesis, skeletal muscle weakness, and parkinsonism. Autosomal recessive inheritance was suggested by many consanguineous marriages, although a dominant disorder could not be excluded. No linkage to known progressive external ophthalmoparesis locus was found. The presence of cytochrome c oxidase-negative ragged-red fibers, biochemically reduced respiratory chain complexes, and multiple mitochondrial DNA deletions in muscle biopsies from four patients suggested a new mitochondrial disorder of intergenomic communication.

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Clinical manifestations of the CNS in the heterogeneous group of the “mitochondrial encephalomyopathies” include epilepsy, strokelike episodes, cerebellar ataxia, and, less frequently, extrapyramidal signs. This heterogeneity is associated with both nuclear and mitochondrial DNA (mtDNA) mutations.<sup>1</sup>

We report a large family from Libya in which several members had a multisystem disorder mainly characterized by the concomitant occurrence of par-

kinsonism and a mitochondrial myopathy affecting ocular and skeletal muscles in association with multiple mtDNA deletions.

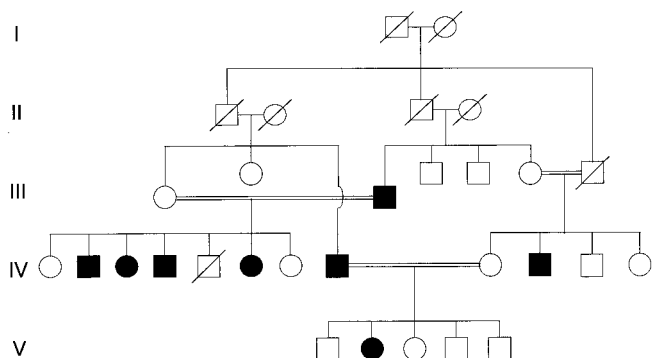
**Patients and methods.** The family was investigated by interviews and by neurologic examination of seven clinical

Neurological Institute (Drs. Casali, Santorelli, Fortini, Damiano, and Amabile) and Departments of Neurosciences (Drs. Bonifati, Fabbrini, Locuratolo, Vanacore, Pierallini, and Meco) and Experimental Medicine and Pathology (Dr. D'Amati), “La Sapienza” University, Rome; Telethon Institute for Genetics and Medicine (Drs. Casari and Patrignani), Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Hospital Saint Raffaele, Milan; Department of Molecular Medicine (Drs. Santorelli and Carrozzo), IRCCS Ospedale Bambino Gesù, Rome; and NEUROMED (Dr. Pierelli), Istituto Neurologico Mediterraneo, Pozzilli, Italy.

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**Figure 1.** Pedigree of the Sephardic Jewish family with ocular myopathy and parkinsonism. Black symbols show affected family members; white symbols indicate unaffected members.