Posteroventral medial pallidotomy for treatment of Parkinson’s disease: preoperative magnetic resonance imaging features and clinical outcome

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Object. The goal of this study was to investigate the impact of mild or moderate degrees of degenerative or ischemic encephalopathy on predicting clinical outcome following unilateral posteroventral medial pallidotomy for treatment of advanced Parkinson’s disease (PD).

Methods. Thirty-five patients with PD were studied prospectively. The presence and degree of cortical atrophy, ventriculomegaly, deep white matter lesions (DWML), periventricular lucencies (PVL), and the presence of lacunes and status cribiformis (multiple and bilateral enlarged Virchow–Robin spaces) were determined by magnetic resonance (MR) imaging before the patients underwent stereotactic pallidotomy performed according to a standard protocol. Clinical outcome was measured using a standard battery of tests including application of the Unified Parkinson’s Disease Rating Scale (UPDRS). The preoperative MR imaging features were correlated with UPDRS subscores such as motor “off” score, the activities of daily living (ADL) off score, the off subscore for bradykinesia, the percentage of “on” time dyskinesias, and a global outcome rating. The MR findings were also correlated with the occurrence of side effects. Global outcome was rated as markedly improved in 22 patients (63%) and as moderately improved in 12 patients (34%) 6 months postoperatively. At the 1-year follow-up examination, global outcome in 31 patients was rated as markedly improved in 14 patients (45%), as moderately improved in another 14 (45%), as slightly improved in two (6%), and as worse in one patient (3%). The mean UPDRS motor off score changed from 58.7 preoperatively to 33.2 at 6 months and 33.4 at 1 year (p < 0.0001), the ADL off score from 31.8 to 18.2 at 6 months and 18.6 at 1 year (p < 0.0001), the off score from contralateral bradykinesia from 11.6 to 5.6 at 6 months and 4.1 at 1 year (p < 0.0001), and the percentage of awake time with dyskinesias from 37.4 to 17.4% at 6 months and 21.1% at 1 year (p < 0.0001). The presence of mild or moderate degrees of cortical atrophy, PVL, and DWML had no effect on clinical outcome. Patients with status cribiformis and those with lacunes tended to show comparatively less improvement in the UPDRS ADL off score (p = 0.014 and p = 0.016, respectively) at 6 months. This tendency was also present in patients with status cribiformis 1 year postoperatively (p = 0.046). Patients with both status cribiformis and lacunes had a higher incidence of transient altered mental status immediately postoperatively (p = 0.05).

Conclusions. Mild-to-moderate degrees of cortical atrophy, ventriculomegaly, and ischemic encephalopathy do not predispose patients to less favorable outcomes following unilateral pallidotomy. Patients with both status cribiformis and lacunes have a higher risk of transient side effects; however, with regard to clinical outcome, these patients should not be denied surgical treatment.

Key Words • pallidotomy • Parkinson’s disease • stereotactic surgery • magnetic resonance imaging • clinical outcome

We are currently witnessing a resurgence in the surgical treatment of Parkinson’s disease (PD) . Recent advances in understanding the functional anatomy, neurophysiology, and pathophysiology of the basal ganglia and refinements of stereotactic techniques have furthered the role of posteroventral medial pallidotomy as a therapeutic option for advanced PD. Pallidotomy has been found to be efficacious for a variety of parkinsonian symptoms including contralateral tremor, bradykinesia, and rigidity. Favorable results are also obtained in patients with levodopa-induced dyskinesias and axial symptoms such as postural instability and gait disturbance. Several aspects, however, need further study. In particular, it is unclear how long these beneficial effects last, whether pallidotomy is superior to other functional stereotactic procedures, and which patients are the best candidates.

In general, it is thought that PD patients with ischemic or degenerative encephalopathy enjoy less benefit and have a higher complication rate after functional stereotactic surgery. However, there are few data available on the relationship between surgical outcome and baseline imaging studies. It is not known whether asymptomatic patients in whom imaging demonstrates mild-to-moderate degrees of cortical atrophy, ventriculomegaly, and ischemic white matter disease have a less favorable outcome or a higher frequency of side effects. In this prospective study, we investigated the impact of subclinical degenera-
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Clinical Material and Methods

Patient Population

The database for this study was composed of 38 consecutive patients who underwent microelectrode-guided posteroventral pallidotomy for the treatment of advanced PD in the period from August 1995 to May 1996 at The Methodist Hospital, Baylor College of Medicine. The major criteria for pallidotomy included the presence of levodopa-induced dyskinesias and disabling bradykinesia that was partially refractory to medical treatment. Patients were excluded if they were older than 75 years of age and if they had significant medical disease; alcohol or drug abuse; evidence of marked cerebral atrophy; hydrocephalus; or severe vascular encephalopathy on preoperative MR imaging; advanced dementia; major depression; Hoehn and Yahr Stage V when “on”; and the presence of features suggestive of other parkinsonian syndromes.29,39 Three of the 38 patients were not included in this analysis: in two patients there was no long-term follow-up review and in one patient the pallidal lesion involved the lateral and medial pallidum on the MR image obtained immediately postoperatively, but was confined to the lateral pallidum on the 6-month postoperative MR image. The latter patient experienced only transient clinical benefit from pallidotomy. There was thus a total of 18 men and 17 women included in the study. The mean age of the patients at the time of the operation was 60 years (range 44–75 years). Twenty-seven patients underwent left-sided and eight patients right-sided pallidotomies. Only unilateral procedures were performed.

Clinical Assessment and Follow-Up Review

All patients underwent preoperative MR imaging examinations and formal clinical assessments preoperatively, at 2 weeks and at 3 months postoperatively, and subsequently at 3-month intervals. For the present analysis, clinical outcome measures obtained at 6 months and at 1 year were used. Two patients included in this study were not available for the 6-month follow-up review. Their 9-month follow-up data, which did not significantly differ from their 3-month follow-up data, were therefore used. For the 1-year follow up, detailed formal assessments were available in 31 patients.

Standardized clinical assessments included: the Unified Parkinson’s Disease Rating Scale (UPDRS),32 Schwab and England scores, Hoehn and Yahr staging, movement and reaction times, and a battery of neuropsychological tests. The UPDRS evaluations were performed when the patient was in the “off” state (12 hours after the last dosage of levodopa) and during the “best on” state. All evaluations were performed by members of the neurology faculty in the Movement Disorders Clinic.

The UPDRS scores used for this analysis include the motor off score, the activities of daily living (ADL) off score, the off subscore for appendicular bradykinesia (scores 23–26) contralateral to the side of surgery, and the percentage of awake time with dyskinesias. Global patient outcome was rated using a five-point scale by both the evaluating neurologist and the patients: 0 indicated worse; 1, unchanged; 2, slightly improved; 3, moderately improved; and 4, markedly improved.

Magnetic Resonance Imaging Examination

Preoperative MR imaging examinations were performed using a 1.5-tesla imaging system (Signa; General Electric Medical Systems, Milwaukee, WI); the sequences included multiplanar T₂-weighted fast spin–echo (FSE) sequences (TR = 3083–5816 msec, TE = 85–95 msec), T₁-weighted FSE sequences (TR = 500–700 msec, TE = 11 msec), and proton density–weighted sequences (TR = 2083–2200 msec, TE = 34 msec). Slice thickness varied between 3 and 5 mm in different sequences with interslice gaps of 1 to 1.5 mm. All MR images were analyzed independently by two investigators.

The degree of cortical atrophy was determined by the width of the frontoparietal sulci at the vertex. Cortical atrophy was assessed using a four-point scale consisting of 0 for normal, 1 for mild, 2 for moderate, and 3 for severe (Fig. 1). Ventriculomegaly was also evaluated using a four-point scale ranging from 0 for normal to 3 for severe.
severe. The width of the third ventricle was measured in millimeters. In addition, the ratio of the maximum width of the anterior horns of the lateral ventricle to the maximum width of the skull (measured by the distance between internal tables) was calculated.

The presence of white matter disease was evaluated separately for periventricular lucencies (PVL) and deep white matter lesions (DWML) on the basis of rating criteria reported previously. The severity of PVL was assessed using a four-point scale with the following specific descriptives: 0 indicated normal (none or very small caps or rims); 1, mild (caps or rims \(\leq 5\) mm); 2, moderate (caps or rims \(> 5\) mm); and 3, severe (large halo). The presence of DWML was rated as: 0 for normal (none or only a few punctate lesions); 1 for mild (one or two foci with none \(> 5\) mm); 2 for moderate (three or more foci or beginning confluent foci); and 3 for severe (confluent lesions or diffuse white matter lesions). The grading in two patients is demonstrated in Fig. 2. In addition, the presence or absence of both lacunes and “status cribriformis” (defined as multiple and bilateral enlarged Virchow-Robin spaces) was noted (Fig. 3).

**Surgical Procedure**

After local anesthesia had been induced, all patients underwent unilateral microelectrode-guided stereotactic pallidotomy. A Leksell G frame was used. Stereotactic computerized tomography (CT) scans were obtained using a helical CT scanner (General Electric Medical Systems). The initial target was located 19 to 21 mm lateral and 4 to 5 mm below the anterior commissure–posterior commissure line and 2 to 3 mm anterior to the midcommissural point. The CT coordinates were translated to frame coordinates and checked on interactive axial, coronal, and sagittal CT images for their proximity to the choroidal fissure.

Microelectrode recording and macrostimulation were used to delineate the target further. Operative techniques are described in detail elsewhere. When the initial tract was judged to be satisfactory, no additional tracts were made. In the majority of patients, one or two pathways were investigated. The first lesion was placed within 1 mm of the ventral pallidal border. One to three lesions were made within a distance of 3 mm by using a 1.1-mm unipolar electrode with a 3-mm uninsulated tip heated to 75°C for 60 seconds. The patients were monitored intraoperatively for contralateral motor function, speech, and visual field deficits.

**Statistical Analysis**

For the purpose of correlative analysis between the preoperative MR imaging findings and clinical outcome, an index was calculated for the relative change of individual clinical scores. The “improvement index” for an outcome measure was obtained by dividing the difference between the preoperative and postoperative scores by the preoperative score in the following form:

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\text{Improvement Index} = \frac{\text{postoperative score} - \text{preoperative score}}{\text{preoperative score}}
\]

The improvement index would therefore be represented by a value ranging between 0 and 1 (0.00 = no improvement and 1.00 = maximum hypothetical benefit). Statistical analysis was performed using commercially available computer software (SigmaStat; Jandel Scientifics, San Rafael, CA). Statistical analyses included the Pearson product moment correlation, one-way analysis of variance, the chi-square test, and Fisher’s exact test.

**Results**

**Clinical Outcome**

Confirmation of the lesions by postoperative MR studies and detailed analyses of clinical outcome are described elsewhere. The lesion was located in the posteroven-tral medial pallidum in all cases. No lesion was identified in three patients 6 months postoperatively, despite sustained clinical improvement. Contralateral parkinsonian symptoms and levodopa-induced dyskinesias were improved in all patients immediately postoperatively. The postoperative UPDRS subscores at 6 months were markedly improved compared with preoperative scores for all outcome measures used in this study. The mean values of the UPDRS scores, including preoperative mean, 6-month postoperative mean, improvement index, and p value, respectively, for the different measures were as follows: motor off score 58.7, 33.2, 0.43, p < 0.0001; ADL
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off score 31.8, 18.2, 0.43, p < 0.0001; and contralateral bradykinesia off score 11.6, 5.6, 0.52, p < 0.0001. The score for percentage of awake time with dyskinesias was also improved at 6 months postoperatively compared with preoperatively (37.4%, 17.4%, 0.53, p < 0.0001). The global patient outcome was rated by the evaluating neurologist as markedly improved in 22 patients (63%), moderately improved in 12 patients (34%), and only slightly improved in one patient (3%). The last patient rated his own condition as unchanged. At the 1-year follow-up review, the means for the corresponding UPDRS measures, including 1-year postoperative mean and p value, as compared with the preoperative score, were: motor off score 33.4, p < 0.0001; ADL off score 18.6, p < 0.0001; contralateral bradykinesia off score 4.1, p < 0.0001; and percentage of awake time with dyskinesias 21.1%, p < 0.0001. Global outcome at 1 year was rated as markedly improved in 14 patients (45%), as moderately improved in another 14 patients (45%), as slightly improved in two patients (6%), and as worse in one patient (3%). In retrospect, the latter patient most probably did not suffer from idiopathic PD.

Transient side effects occurred in five patients (14%) in the early postoperative period. Four patients exhibited altered mental status manifest by varying degrees of disorientation, confusion, sleepiness, or agitation. One patient displayed a mild Broca’s aphasia secondary to a small ischemic infarction involving the corona radiata, the periventricular white matter, and the dorsal thalamus. All adverse effects resolved completely. In two patients the initial operation was discontinued before the therapeutic lesion could be placed. In one of these patients, this was due to technical problems, whereas the other patient suffered a vasovagal syncopal episode. Both patients underwent successful pallidotomy during a second session.

Preoperative MR Imaging Features

The distribution of preoperative scores for cortical atrophy, ventriculomegaly, DWML, and PVL is shown in Table 1. The majority of patients had no or mild cortical atrophy and ventriculomegaly. In accordance with our protocol for patient selection, no patient had severe cortical atrophy or severe ventriculomegaly. Nine patients (26%) had lacunes and five patients (14%) had mild or moderate status cribriformis. The mean width of the third ventricle was 4.4 mm (range 1–7 mm). The mean ventricular ratio was 0.28 (range 0.19–0.35).

Preoperative MR Imaging Features and Clinical Outcome

There was no correlation between any of the preoperative MR imaging findings and global improvement scores at 6 months and at 1 year postoperatively. There was also no correlation between the width of the third ventricle and the change in clinical outcome measures. Furthermore, there were no significant associations between the severity of cortical atrophy, the severity of DWML and PVL, and the changes in clinical condition. The ventricular ratio and the degree of ventriculomegaly did not correlate with changes in the UPDRS motor off score, the ADL off score, and the bradykinesia off score. Both MR imaging parameters did, however, correlate negatively with improvement in the percentage of awake time with dyskinesias. This correlation was significant for the ventricular ratio (p = 0.031 at 6 months and p = 0.013 at 1 year), although it did not reach significance when the distribution of the degree of ventriculomegaly was assessed (p = 0.086 at 6 months and p = 0.254 at 1 year).

There were no significant associations between the presence of either lacunes or status cribriformis with changes in the UPDRS subscores except for the ADL off score. Patients with either lacunes or status cribriformis tended to show less improvement in the ADL off scores at the 6-month follow up (lacunes, p = 0.016; status cribriformis, p = 0.014). At the 1-year follow up, this association was still significant for the presence of status cribriformis (p = 0.046), but not for the presence of lacunes (p = 0.217).

Preoperative MR Imaging Features and Side Effects

A transiently altered mental status was the most frequent and clinically important side effect seen in this study. There were no correlations between the degree of cortical atrophy, ventriculomegaly, DWML and PVL, and side effects following pallidotomy. Patients with status cribriformis displayed a trend toward occurrence of altered mental status immediately following pallidotomy (p = 0.089). Although the presence of lacunes alone was not associated with altered mental status (p = 0.267), the presence of both status cribriformis and lacunes was associated with a higher risk for the development of postoperative altered mental status (p = 0.05).

Discussion

In this study, almost all patients benefited from the surgical procedure: global clinical improvement was rated as marked in 22 patients (63%) and moderate in 12 patients (34%) 6 months after unilateral pallidotomy. There was a slight change in the distribution of global clinical outcome at 1 year, with 45% of patients enjoying marked improvement and 45% of patients having moderate improvement. Because some patients had greater improvement in their clinical symptoms at 1 year when compared with the 6-
month postoperative evaluation, the mean of the UPDRS subscore was not substantially altered. The present results are comparable to those of other recent studies. 3,8,16,53 Pallidotomy appears to be efficacious in almost all appropriately selected patients and is associated with a relatively low risk when using modern surgical techniques. We believe that microelectrode guidance further reduces the rate of possible adverse sequelae. Microelectrode recording and microstimulation make it possible to place the lesion at the ventral pallidal border while avoiding damage to the optic tract.

Degenerative and vascular encephalopathy are thought to have a negative impact on clinical outcome after functional stereotactic surgery. 6,13,14,31,36 Such a relationship is obvious in patients who are demented or who suffer from disability secondary to the underlying encephalopathy. Therefore, these patients usually are excluded from surgical treatment protocols. With the advent of MR imaging, however, it has been shown that asymptomatic white matter lesions are present in healthy elderly individuals as well as in patients with various neurodegenerative diseases. 5,7–11 Both the incidence and the severity of white matter lesions increase with age and are often associated with cardiovascular risk factors. 17–19 Chronic vascular insufficiency frequently accounts for white matter changes seen on MR images in elderly patients. 4,23,31,43

Varying degrees of ventriculomegaly and periventricular lesions and DWMLs 3,8,38 have been described in neuroimaging studies of PD patients. Other reports have noted the occasional presence of lacunes and dilation of the perivascular spaces (status cribiformis) in the basal ganglia in elderly PD patients. 12,42 One study demonstrated a higher frequency and extent of PVL in patients with PD than in healthy age-matched subjects. 38 Takeuchi, et al., 45 found at least one lacune in 19 of 31 elderly PD patients.

The occurrence of radiographic correlates of vascular and degenerative encephalopathy was relatively lower in our patients than in previous reports 38,42 because of the exclusion of patients with severe encephalopathy. Nevertheless, MR imaging frequently demonstrated mild or moderate encephalopathy in this population of elderly patients. As demonstrated, however, such asymptomatic findings have little or no impact on clinical outcome after unilateral pallidotomy. Neither the degree of cortical atrophy nor the presence of DWML affected clinical outcome. Also, the degree of ventriculomegaly and the ventricular ratio did not correlate with outcome measures, except for improvement of dyskinesias. Because only one of the two parameters showed a significant correlation, the relevance of this finding remains unclear.

Although the presence of status cribiformis or lacunes did not interfere with improvement in scores measuring motor function, it negatively affected the improvement in ADL in the off state. This tendency was significant for both conditions at the 6-month follow up and also for status cribiformis at 1 year postoperatively. This association may be related to the fact that the UPDRS ADL score is used to evaluate functions such as swallowing, dressing, speech, and others that may be impaired by diseases other than PD. Status cribiformis and lacunes as manifestations of cerebrovascular disease per se may account for additional baseline disability. Because side effects, overall, were rare in our series, the findings reported here should be interpreted with caution. Mild degrees of cortical atrophy, ventriculomegaly, and DWML and PVL do not appear to predispose patients to a higher frequency of side effects. However, status cribiformis alone or in conjunction with lacunes may increase the risk for postoperative transient altered mental status. Nevertheless, patients who suffered from transient altered mental status enjoyed relief from their parkinsonian symptoms after they recovered. The presence of status cribiformis and lacunes should, therefore, not exclude these patients from unilateral pallidotomy. Bilateral functional stereotactic procedures, however, may potentiate the risk in this subgroup.

Conclusions

Unilateral posteroventral pallidotomy is a useful procedure for treatment of motor dysfunction in patients with advanced PD. Mild-to-moderate correlates of degenerative or vascular encephalopathy, as assessed by MR imaging, have little or no effect on benefit from surgery. Patients and relatives of patients with status cribiformis and lacunes should be counseled appropriately.

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