

Lesion Surgeries

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EARLY SURGICAL EXPERIMENTS AND SUCCESS OF SURGERY FOR MOVEMENT DISORDERS

The following description is of case VI from James Parkinson's 1817 essay on paralysis agitans (1):

About a year since, on waking at night, he found that he had nearly lost the use of the right side, and that his face was much drawn to the left side. His medical attendant saw him the following day, when he found him languid, with a small and quick pulse and without pain in the head or disposition of sleep. Nothing more therefore was done . . . and in about a fortnight the limbs had entirely recovered from their palsied state. During the time of their having remained in this state, neither the arm nor the leg of the paralytic side was in the least affected with the tremulous agitation; but as the paralyzed state was recovered, the shaking returned.

This may be the first description of a cerebral insult that alleviated an extrapyramidal sign. Interestingly, 175 years later this phenomenon is still being described (2). Early attempts to treat tremor by open resection of

motor and premotor cortex resulted in the substitution of disabling extrapyramidal symptoms with disabling hemiparesis (3,4). A major advance came about with the publications of Russell Meyers in 1942 and 1951, showing that surgical resection of the head of the caudate nucleus and pallidofugal fibers (5,6) could resolve tremor and rigidity without inducing paresis. This paved the way for the next 20 years of experimental basal ganglia lesion surgery as treatment for extrapyramidal syndromes. Surgical precision was improved and comorbidity reduced with the development of the stereotaxic technique (7). Subsequently, stereotaxic chemopallidectomy using procaine oil (8), alcohol (9), and pallidal electrocoagulation (10,11) were reported to effectively improve tremor and rigidity.

It is important to note that at this time results were not reported in an objective manner and lesion locations within the pallidum were not precisely documented. The target was the anterodorsal pallidum, a target now proposed to be part of the associative circuits involved in motor control (12). The benefit of a more ventral lesion had already been documented with lesions, which included the ansa lenticularis (13). This group also reported the benefit from more posterior lesions by showing that five patients, who had gained only temporary relief from tremor from anterodorsal pallidotomy, gained sustained antitremor benefits when their lesions were extended by 4–6 mm posteriorly (14).

In an attempt to study and improve outcomes, Svennilson et al. varied the position of their lesions in the first 32 cases from their cohort of 81 patients between 1953 and 1957 and showed sustained improvements in rigidity and tremor by 79 and 82%, respectively, when the lesion was in the posteromedial aspect of the pallidum (15). They also reported additional benefit to general motor function, as assessed by their patients' ability to return to work (25%) or become independent in activities of daily living (37%).

During this era, other surgical groups were varying lesion locations not just within the pallidum but within the basal ganglia. Some early evidence suggested the superiority of thalamotomy in resolving tremor and rigidity (9,16). These reports were later extended to specify ventrolateral and ventral intermediate thalamotomy (17,18). In 1967, the introduction of levodopa as effective antiakinetic and antitremor therapy for parkinsonism (19) led to a major worldwide reduction in the use of pallidotomy and thalamotomy to treat parkinsonism. In today's practice, lesion surgery has reemerged with a new role as a result of identification of new indications and new targets within the basal ganglia (20–22). We shall review some general principles that apply to all patients considered for lesion surgery of the pallidum, thalamus, and subthalamus before discussing the merits of lesions at each target site. This chapter will not consider gamma-knife lesions.

PATIENT SELECTION

Modern Indications for Surgery for Parkinson's Disease

The modern incentive to reevaluate surgical therapy for Parkinson's disease (PD) has been driven by the realization of the inadequacy of chronic dopaminergic replacement as a main strategy of treatment, namely that:

1. Levodopa treatment is associated with the development of motor fluctuations and dyskinesia (23,24) in about 50% of patients after 5 years of treatment (25). In early PD, these side effects are generally associated with peak plasma levels of drugs and so can usually be controlled by adjusting dose size and frequency. With disease progression, the "therapeutic window" narrows and dyskinesia may develop during any period of benefit or biphasically and cannot be controlled by dosing changes. At this stage, neither parkinsonism (akinesia and tremor) nor drug-related side effects (dyskinesia and fluctuations) can be managed optimally and surgery is warranted. In this scenario, the primary objective of surgery is to alleviate dyskinesia and fluctuations. The post-operative dose of dopaminergic medication will be determined by the patient's clinical needs. This may be less than that required before surgery. However, in some patients (depending on the procedure) it may be unchanged or even higher.
2. Some patients show effective initial response to dopaminergic medication, which becomes less effective with disease progression, such that in time the dose of levodopa or dopamine agonists required to provide symptomatic relief from akinesia or tremor is associated with the development of unacceptable peak dose effects, such as postural hypotension or behavioral disturbances and psychosis. Other unresponsive symptoms can include painful cramps and dystonia. In this scenario, the objective of surgery is to act as an adjunct to antiparkinsonian medication to allow the patients to obtain effective antiparkinsonian relief from the combination of surgery and lower doses of dopaminergic drugs that do not induce undesirable side effects.

Often patients present with a mixture of these two indications.

Entering a Patient for a Surgical Procedure

Prior to enrolling a patient into a surgical program, it is generally recommended that patients be assessed by a neurologist with experience in movement disorders since it is essential to document that the patient does

indeed have PD and not a parkinson-plus syndrome, such as multiple system atrophy, progressive supranuclear palsy, or vascular parkinsonism. There have been a few case reports of the use of lesion surgery in the management of these parkinson-plus syndromes, and their success rates are generally disappointing (26,27). Additionally, it is necessary to show that a patient has a good response to dopaminergic drugs (see Fig. 1), since the antiparkinsonian benefit from levodopa correlates with the antiparkinsonian response to surgery (with the exception of tremor). A standard levodopa challenge test, as described in the Core Assessment Program for Intracerebral Transplantations (CAPIT) (28) or Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT-PD) (29), is one prognostic indicator of a patient's short-term response to a successful surgical procedure (30). A history of unresponsiveness to levodopa may also be an indicator that the patient is suffering from a parkinson-plus syndrome.

Some patients or physicians seek referral for surgery before adequate trials of available medication have been carried out. At times this is due to inadequate experience in the management of PD, and at other times it is due to a misguided desire to avoid complications of dopaminergic medication. Patients should receive appropriate trials of available medication before considering invasive and potentially complicated surgery.

Many patients in late-stage disease may have cognitive or active psychiatric symptoms. These patients should be excluded from surgery. There are no absolute contraindications to lesion surgery over and above those of general surgery as determined by the patient's general medical state. However, patients with a significant dementia or cortical atrophy may have less benefit from surgery and may cognitively decompensate postoperatively (27,31). Centers should obtain formal neuropsychometric testing prior to surgery and utilize these results in considering surgical candidacy.

Speech, swallowing, and gait disturbances are common in advanced PD. Although these symptoms are less likely to improve following surgery and indeed may deteriorate postoperatively, especially following bilateral procedures (32–35), they should be recognized as relative, and not absolute, contraindications. For example, a patient who already has a percutaneous feeding gastrostomy, should not be denied a surgical therapy solely on the basis of the severity of the dysphagia, which may deteriorate postoperatively, since it is likely that the feeding tube will still remain in situ postoperatively.

Considering Lesion Surgery over Deep Brain Stimulation

Several open trials have demonstrated the efficacy of deep brain stimulation (DBS) of the basal ganglia nuclei in the treatment of parkinsonism and the

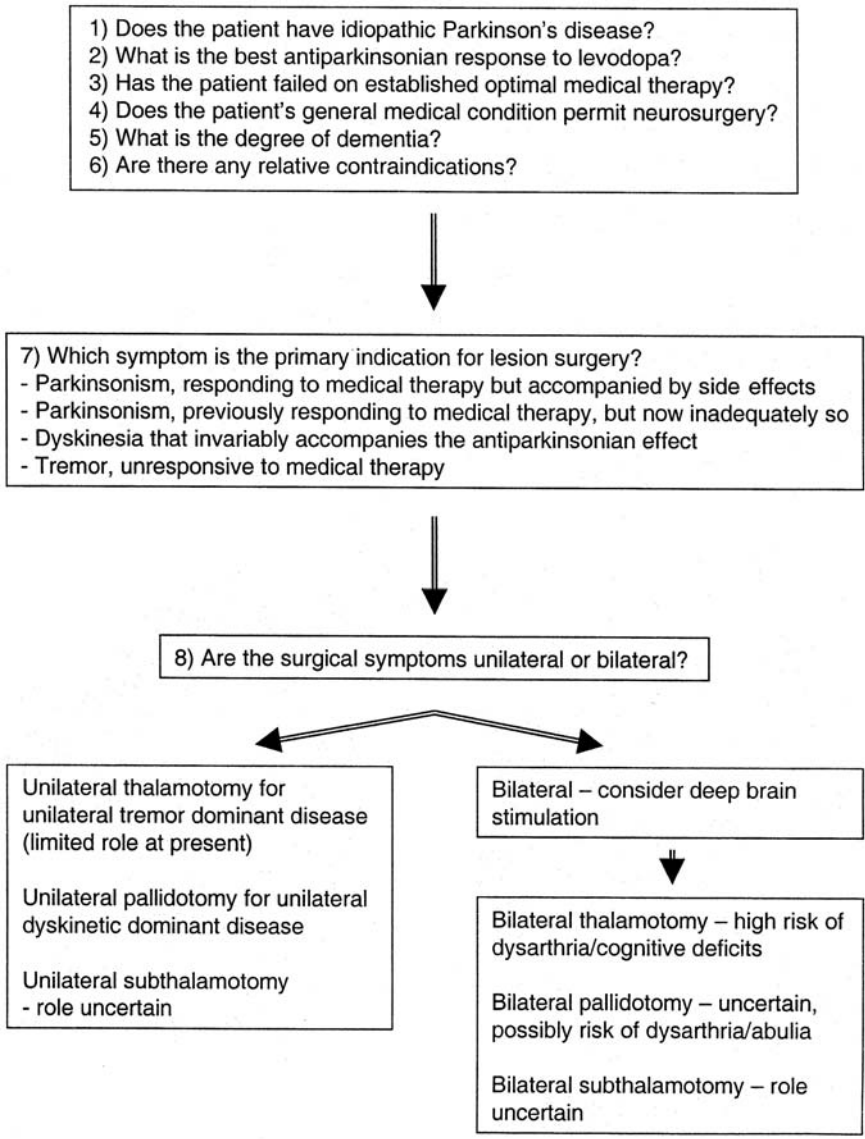


FIGURE 1 Factors in deciding on lesion surgery for a patient with Parkinson's disease.

resolution of levodopa-induced dyskinesia (36–38). Only one included a double-blind evaluation of symptoms (39). Although there are no direct

comparative trials of the safety of DBS and lesion surgery, it is generally accepted that DBS is effective, allows patients to lower the overall drug requirement, and may involve less permanent risk since the target is not electrocoagulated. This makes the consequences of a misplaced target reversible with DBS, but irreversible with lesion surgery. This is most important when considering bilateral procedures, since the risks of dysphasia, dysarthria, dysphagia, and cognitive deficits are increased in bilateral procedures (32–35). Although there are no blinded, evidence-based trial data to indicate which type of surgery to offer, the following guidelines can be considered:

1. If a patient requires a bilateral procedure from the outset, then bilateral DBS is usually preferred over bilateral lesion surgery. This is the case for most patients with advanced PD.
2. If a patient has already had a unilateral procedure (whether a lesion or DBS) and requires a second procedure in the other hemisphere, then DBS should be considered in preference to a lesion since any new side effects from the second procedure are more likely to be reversible.
3. If a patient is considered for a unilateral procedure from the outset, then lesion surgery and DBS should be considered according to the preference of the patient and the surgical center.

The longest reported results are 10 years for pallidotomy (40) and 13 years for thalamotomy (18). Despite the untested longer-term safety of either lesion surgery or DBS, there are some general advantages of lesions compared with DBS. First, when health resources of either an individual or a health care provider are limited, it is usual to adopt the more economical option. Lesion surgery avoids the cost of the hardware, the potential cost of repeatedly replacing the implantable pulse generators due to battery failure, and the manpower expenses for programming the stimulators. Second, for patients who live in areas that have no local expertise in maintenance of deep brain stimulators, the placement of a lesion may avoid frequent journeys to a neurosurgical center for stimulator programming. Programming is required periodically throughout the time the stimulators are in place. Third, it is possible that with time we shall discover more unique but disastrous complications of stimulators interacting with other electrical systems, such as diathermy for dental treatment (41). Finally, DBS electrodes can fracture, become infected, cause skin erosion, or the battery lifetime may become impractically short. In these instances, a lesion may be the only alternative for patients for whom DBS is no longer suitable for technical reasons. Oh et al. described two patients in whom therapy was changed from DBS to a lesion because one patient needed four battery

replacements in 5 years while the other developed skin erosions over the electrode leads (42).

PRACTICAL ISSUES IN THE CHOICE OF A TARGET

The three main basal ganglia targets are the pallidum, thalamus, and subthalamic nucleus, and each has been lesioned unilaterally and bilaterally. In considering the results from different reports, it should be emphasized that the methods of clinical assessment, site of target, method of target localization, and method of target confirmation have varied widely among centers. These factors probably account for the differences in clinical outcome across centers. The most comprehensive assessment would have to include:

1. Pre- and postoperative blinded evaluation of objective rating scales, such as the Unified Parkinson's Disease Rating Scale (UPDRS) Hoehn and Yahr, timed motor tests (28,29), dyskinesia rating scales (43), and cognitive rating scales.
2. Identification of the anatomical target by computed tomography (CT), magnetic resonance imaging (MRI), or CT-MRI fusion.
3. Identification of the physiological target by microrecordings and macrostimulation.
4. Verification of lesion size and location postoperatively by volumetric MRI.
5. Long-term follow-up.

It is no wonder, therefore, that reports originating from different centers are rarely directly comparable. The method of target localization can be primarily based on anatomical landmarks, such as stereotaxic CT or MRI coordinates or combined CT-MRI fusion. Most groups will also use macrostimulation at the target site prior to lesioning to check for adverse effects, which most commonly manifest as contraction of the face, arm, or foot, sensory changes, ocular deviations, phosphenes, or speech arrest.

Some centers also rely on intraoperative microelectrode recordings from the target site. For thalamotomy, this is used to demonstrate oscillations synchronous with tremor ("tremor cells"), which aid the surgeon in finding the correct target and avoiding the ventral caudal (VC, sensory) nucleus. For pallidotomy and "subthalamotomy," tremor may not be the primary indication for surgery and these oscillations may not be detectable. In these instances, there are other advantages of using intraoperative microelectrode recordings. First, the identification of cells that change their firing rates in response to active or passive movements will confirm that the tip of the electrode is at the sensorimotor region of the

target zone. This method of electrophysiological mapping increases the probability that the lesion is placed in the sensorimotor region of the pallidum or subthalamus and decreases the probability that the lesion is placed in the nonmotor region of the target, where there may be less clinical benefit and potentially greater adverse effects. Second, identification of the boundaries of the pallidum and subthalamus allows the lesion to be placed away from the optic tract and internal capsule, reducing the likelihood of undesirable effects. This is especially important for placement of very ventral pallidal lesions where CT alone, MRI alone, or CT-MRI fusion may not be sufficiently accurate to avoid the optic tract (44). Third, recording the response rates of neurons in these nuclei has aided our understanding of PD (45–47) by providing direct human evidence that the overactivity of internal pallidal and subthalamic neurons contributes to the pathophysiology of parkinsonism.

UNILATERAL PALLIDOTOMY

Posteroventrolateral, Posteroventromedial, or Pallidoansotomy?

The era of modern pallidotomy started when Laitinen reexplored Leksell's pallidotomy for patients who were refractory to medical therapy (48). In this first study of 38 patients, he confirmed that the optimal target should be in the posteroventral, rather than anterodorsal, pallidum. He showed that there was complete or almost complete relief of rigidity and hypokinesia (92% of patients), tremor (81% of patients), and an improvement in levodopa-induced dyskinesia. These lesions were placed 16–24 mm lateral to the midline but were associated with a 14% risk of damage to the optic tract, which could be located as far as 21 mm lateral to the midline. In his subsequent series, the laterality was increased to 24–27 mm from the midline in the posteroventrolateral pallidum, with particular attention paid to “minimizing damage to the medial pallidum” (27). It is hypothesized that the beneficial effect is the result of interruption of the direct striatopallidal and indirect pallidosubthalamic afferents to the internal pallidum. In this manner it is argued that pallidotomy “releases the medial pallidum” from abnormal regulation by the external pallidum and subthalamus. These series should be considered distinct from other contemporary series, in which the objective of pallidotomy is to ablate and reduce the overactivity of the medial pallidum.

Many groups have generally reproduced the clinical findings in open studies in which the anatomical target was located within the posteroventral pallidum by anatomical guidance (49–52). Other groups have extended the

understanding of the pathophysiology of parkinsonism by using microelectrode recordings to map the sensorimotor region of the internal pallidum during functional neurosurgery and have argued that optimal clinical response is best achieved by placing the lesion at the neurophysiological target (45,46,53–57). The caudal internal pallidum has been shown to contain cells that directly respond to active and passive manipulation of limb movements (45,58) and is thought to represent the sensorimotor region of the internal pallidum. The location of the human sensorimotor region of the internal pallidum is in general agreement with that from the parkinsonian primate (59). It is somatotopically arranged (60), although the boundaries between one area and the next are less distinct than in the cortex. However, there is some controversy whether clear somatotopy can be demonstrated in parkinsonian humans at the time of pallidal microrecording. Successful lesions should theoretically encompass the sensorimotor region of the internal pallidum. Bakay et al. reported that they have increased the mediolateral extent of their pallidotomy to maximize benefit (61). As mentioned below, some authors have argued that the ideal lesion should be made in the extreme ventral pallidum attempting to include the ansa lenticularis (62) (i.e., pallidoansotomy). However, in the nonhuman primate it has been shown that most of the sensorimotor output of the internal pallidum to the thalamus comes directly across the internal capsule via the lenticular fasciculus (63), and so purposefully lesioning the ansa may be both ineffective and unnecessarily risky since it is very close to the optic tract.

Trial Results

The results of only one randomized, single-blind trial of pallidotomy have been published (64). In this study, 37 patients, who were matched for age and severity of PD, were randomized to receive either unilateral pallidotomy within one month ($n=19$) or maximal medical therapy for 6 months ($n=18$). While the nonoperated group showed an 8% deterioration of median UPDRS motor scores and no change in dyskinesias, the operated group showed 31% and 50% improvements in parkinsonism and dyskinesia scores, respectively.

There have been two nonblinded studies of patients treated by pallidotomy compared with a medically treated group (53,65), with each study demonstrating the benefits of pallidotomy. The numerous other open-label nonrandomized trials (30,46,48,49,51,52,66–77) have generally drawn the same conclusion (Table 1, Fig. 2), indicating that the most dramatic response is the reduction in contralateral dyskinesia by 80–95%, which is sustained for up to 5.5 years (77). The off UPDRS score improves by 24–

TABLE 1 Summary of Large Pallidotomy Series in Order of Study Size^a

Author	n	Surgical method	Main clinical assessment	Follow-up interval	Akinesia (Δ%)	Tremor (Δ%)	Gait (Δ%)	Dyskinesias (Δ%)	Overall mortality (%)	Overall morbidity (%)
Laitinen, 1995 (73)	259 ^b	CT/MRI + MES	"Fair, good, poor"	<48 hours		82% "good"	Not given	Not given	0	7
Kondziolka et al., 1999 (51)	58	MRI + MES	UPDRS	6–24 months	24	50	0	40	0	7
Iacono et al., 1994 (49)	55	MRI + ventriculography + MES	"Minor, good or excellent"	1–24 months	"Excellent"	"Good"	"Excellent"	"Excellent"	0	7
Jankovic et al., 1999 (71)	41	MRI + μER + MES	MT	3 months	24	Not given	Not given	Not given	Not given	Not given
Lang et al., 1999 (74)	40	MRI + μER + MES	UPDRS + Goetz	3–24 months	43	54	42 transient	83	0	38
Alterman and Kelly, 1998 (66)	34	MRI + μER + MES	UPDRS + timed motor tests	6 months	50%	Not given	Not given	"Effectively relieved"	0	10
Masterman et al., 1998 (75)	32	MRI + μER + MES	UPDRS	3–6 months	23 B	43 B	30	61 B	0	16
Hirai et al., 1999 (70)	28	MRI + μER + MES	"Fair, good or excellent"	6 months		Improved B	Dramatic in 8	Improved B	0	0
de Bie et al., 1999 (68)	26	Ventriculography	UPDRS + Goetz	5 months	33	83	38	50	0	50
Shannon et al., 1998 (76)	26	MRI + μER + MES	UPDRS	6 months		26 A + T + R	0	73	4	
Samuel et al., 1998 (30)	26	CT + μER + MES	UPDRS	3 months	24 ^c	33 ^c	7	67	8	
Johansson et al., 1997 (72)	22	CT/MRI + MES	UPDRS v/VAS PLM	12 months	0	0	0	33	0	19 ^d
Samii et al., 1999 (52)	20	CT + MES	UPDRS + GOETZ + PPT	24 months	0	90	0	83	5 ^e	5 ^f
Dalvi et al., 1999 (67)	20	CT-MRI fusion + μER + MES	UPDRS	3–12 months	22 + R	62	0	71	0	
Fine et al., 2000 (77)	20	MRI + μER + MES	UPDRS + Goetz	66 months	18%	65%	43%	71%	Not given	Not given
Baron et al., 1996 (46)	15	CT/MRI + μER + MES	UPDRS	12 months	≥ 50 ^g	100 in 7/8 cases	Not given	100 in 9/10 cases	0	20
Fazzini et al., 1997 (69)	11	CT/MRI + μER + MES	UPDRS	12–48 months	43	Not given	Not given	"Did not return"	Not given	Not given
Laitinen et al., 1992 (48)	38	CT + MES	Writing, drawing, walking in a circle	2–71 months	≥ 40 ^g in 35/36	Excellent in 26/32	≥ 23*	"Greatly improved"	0	22

^aFor comparison, the original series of Laitinen is the final entry. n = number of patients; MES = macroelectrode stimulation at target site; μER = microelectrode recording at target site; MT = finger movement time between two adjacent targets; Goetz = the Goetz dyskinesia rating scale; Δ% = % change; A + T + R = combined score for akinesia, tremor and rigidity reported; + R = combined score with rigidity reported; v/VAS = video and visual assessment scale; PLM = electronic recording of posturolocomotion manual test; PPT = Purdue Pegboard test; B = assumed bilateral as no distinction made between contralateral and ipsilateral score.

^bSome patients had Parkinson-plus syndromes and others had combined pallidotomy and thalamotomy.

^cMarginally significant result.

^d1 patient developed anarthria and 2 patients require reoperation as they had no benefit from the first pallidotomy.

^e1 death two weeks post-operatively secondary to ipsilateral intracerebral haemorrhage.

^f1 patient required re-operation as had no benefit from the first.

^gfigure calculated from a graph in manuscript.

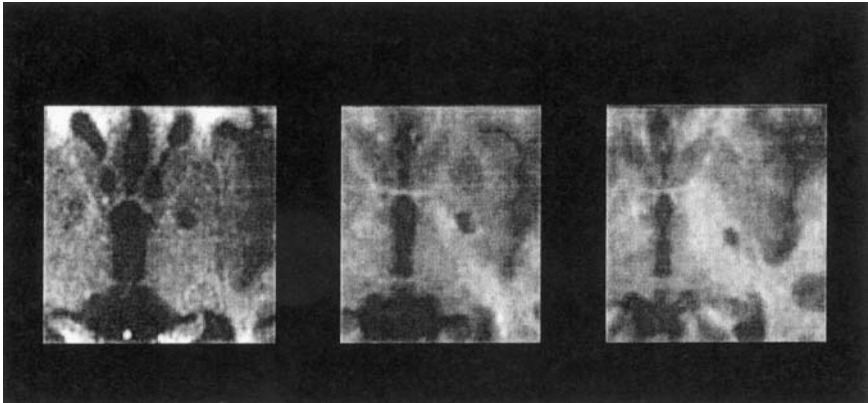


FIGURE 2 MRI scan of unilateral posteroventromedial pallidotomy. (Courtesy of Dr. A. M. Lozano, Toronto Western Hospital, Ontario, Canada.)

37% and declines thereafter to about 18%, although this continues to remain significantly improved at 5.5 years from baseline (57,77). Individual items of contralateral tremor, rigidity, and akinesia generally mirror this response, although the magnitude of the antitremor effect (up to 65%) appears greater and more sustained than that of rigidity (43%) or akinesia (46% at 6 months to 17% at 5.5 years). Despite these sustained differences in UPDRS subset scores, an initial improvement in activity of daily living of 37% is not sustained (77), but results from patient self-assessments imply that patients continue to benefit generally (57). In contrast to contralateral off scores, ipsilateral off scores and both contralateral and ipsilateral on scores are not significantly sustained, although an initial improvement of up to 27% may occur. Ipsilateral on dyskinesia scores appear to be improved initially by 30%. This effect is also decreased with time and is not significant 12 months postsurgery (57).

Despite the reported differences in lesion location, the 10-year effects of Leksell's original series of posteroventrolateral pallidotomy (using anatomical targeting methods and intending to lesion lateral pallidum while causing minimal damage to internal pallidum) are remarkably similar to the long-term responses of posteroventromedial pallidotomy (using anatomical and electrophysiological targeting methods and intending to avoid lateral pallidum while causing maximum damage to the sensorimotor region of internal pallidum).

The responses of axial symptoms and gait are variable. Complex analysis of posturography has shown that an improvement in gait and

posture may be maintained for up to 12 months (78). Three-dimensional motion capture analysis of walking suggests that the effect is mainly due to an improvement in speed of walking (79). More traditional UPDRS gait/postural instability subset scores, however, show only an initial modest improvement (26–37%), which is lost within subsequent years (57,77). It is possible that the effect of pallidotomy on gait may be mediated in part via descending influences on the brainstem, as well as ascending influences on thalamo-cortical circuits (78). Longer follow-up of complex gait analyses is required before reliable conclusions can be drawn.

Complication rates are generally quoted as approximately 5% with transient facial and limb paresis the most common. Hemianopsia or quadrantanopsia are potential complications of lesioning the nearby optic tract. There is a well-documented consistent feature of a mild but asymptomatic decrease in verbal fluency (34), mostly following left-sided unilateral pallidotomy (80). Postoperative weight gain has been described (81). This “side effect” was found in 23% of patients in one study (82). It was highly correlated with the improvement in off motor UPDRS scores but not with changes in energy intake or dyskinesia scores. This suggests that the effect is not purely related to less dyskinesia postoperatively. Some series have reported a higher overall incidence of major complications. In the controlled trial of de Bie et al. (64), 9 of the 19 (47%) operated patients had surgical morbidity (2 major, 4 minor persistent, and 3 minor transient). Lesion locations were not presented, but this level of high morbidity has also been documented by other independent groups (30,76). It is likely that the variability of lesion locations and surgical techniques account for these differences, and this remains one area in need of refinement and agreement across international centers.

Variability of Trial Results

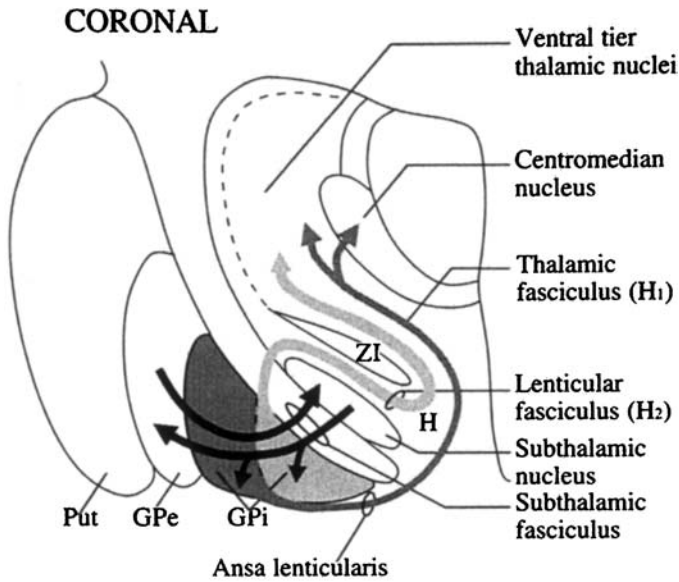
A systematic attempt to correlate outcome with lesion location has been made. Gross et al. studied the variability in lesion location within the ventral pallidum in 33 patients with PD (83,84). Lesions were not distributed randomly within internal pallidum but were distributed along a line running anteromedially-posterolaterally, parallel to the lateral border of the posterior limb of the internal capsule. In this cohort, anteromedial lesions were associated with a greater improvement in dyskinesias while central lesions led to a greater improvement in akinesia scores and gait disturbance (84). This result may partly explain the variable results in resolution of dyskinesia/akinesia among different neurosurgical centers and clearly demonstrates the precision required to perform pallidotomy. This notion is also supported by studies of internal pallidal DBS. Since the clinical

effects of electrode activation are similar to pallidotomy, it is commonly believed that DBS acts by locally inhibiting target nuclei. Studies (85,86) have shown that ventral stimulation leads to resolution of dyskinesias and rigidity with concurrent worsening of akinesia, while stimulation of the most dorsal contacts leads to opposite clinical effects.

Furthermore, both human and primate studies have shown that the discharge rate of the parkinsonian internal pallidal neurons is sustained at a high rate (80 Hz) (45,87). The internal pallidal output via the ansa lenticularis and lenticular fasciculus terminates in the ventral anterior and lateral thalamic nuclei (88) and uses the inhibitory neurotransmitter γ -aminobutyric acid. On the basis of these observations, it is hypothesized that medial pallidotomy would be most effective if the lesion were large enough to include the sensorimotor arm and leg areas and include the neurons that give rise to the ansa lenticularis and lenticular fasciculus (Fig. 3). Such a lesion would interrupt the overactive inhibitory “noisy” outflow of clinically relevant sensorimotor regions of the internal pallidum, thereby disinhibiting the motor thalamus (12). Direct evidence for this is still lacking, but in a retrospective analysis it was documented that lesions were more effective when located within the internal pallidum, and the efficacy was reduced when the lesion encroached on the external pallidum (61). Although now it is generally accepted that the lesion should be in the posterior and ventral pallidum, whether lateral pallidum should be included in the lesion is still controversial. This is likely to remain so until a large data set of clinicopathological cases is gathered worldwide.

There has been recent quantitative evidence supporting the rationale for use of microelectrode recording in guiding lesion placement in pallidotomy. Guridi et al. compared the theoretical target location (obtained from MRI alone) with actual target location (obtained from microelectrode mapping of GPi) in 50 patients who underwent microelectrode-guided internal pallidotomy (56). They showed a maximum discrepancy of 2.3 ± 1.6 mm mediolaterally and 3.0 ± 1.9 mm anteroposteriorly between the anatomical and electrophysiological targets. In only 45% of the patients did the electrophysiological and anatomical targets overlap. Similar posterior and lateral misregistration of the actual target from the electrophysiological target has been described by Tsao et al. (89). These findings imply that surgery based solely on anatomical landmarks may miss the physiological target, even when the lesion is in the correct nucleus.

There remain concerns that the increased number of needle tracts necessary for intraoperative microelectrode recordings increase the overall length of the procedure without clear added benefit and also may increase the overall risk of surgical morbidity from hemorrhage or by increasing the overall lesion volume (the summation of multiple microlesions). To date



HORIZONTAL

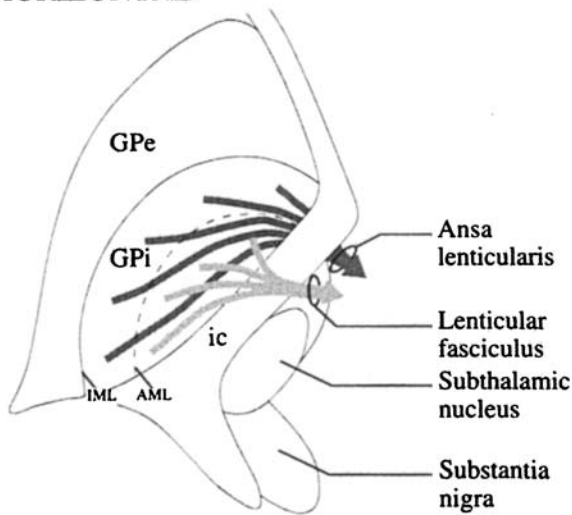


FIGURE 3 Drawing of the coronal and horizontal sections through the human basal ganglia showing the output pathways from the pallidum. Put = putamen, GPe = external pallidum, GPi = internal pallidum, H, H₁, H₂ = fields of Forel, IC = internal capsule, ZI = zona incerta. (From Ref. 125.)

there are no clinical trials demonstrating an additional benefit from the use of intraoperative microelectrode recordings, although there are reports of patients who have undergone a second procedure with intraoperative microelectrode recordings and achieved a better result than from the first procedure, in which a lesion was placed outside the sensorimotor region of the internal pallidum (90). Conversely, there are no studies demonstrating additional morbidity from intraoperative recordings, and so the choice of method of target identification is still largely determined by individual preferences, available equipment, and local expertise.

Another group has specifically targeted only the most ventral region of the posterior pallidum and attempted to produce pallidotomy and ansotomy (62). They have performed 31 pallidotomy/ansotomy operations just 0.5 mm above the optic tract with the entire lesion being situated below the commissural plane. In this series, they described a 63% reduction in “off” parkinsonism and the cessation of contralateral dyskinesia in 21 of 23 patients who had disabling dyskinesias preoperatively. These reports, however, require further validation before general acceptance. It is clear from these variable lesion locations that the optimal target for unilateral pallidotomy remains a matter of controversy and that neither the ventroposterolateral pallidotomy of Laitinen (73), nor pallidoansotomy of Iacono (62), nor the more extensive internal pallidotomy (46,69,74) can fully explain the clinical findings of alleviation in parkinsonism and levodopa-induced dyskinesia concurrently.

BILATERAL PALLIDOTOMY

Laitinen (73) and Iacono et al. (62) reported early good outcomes in 12 and 10 bilaterally operated patients, respectively. There are, however, concerns regarding permanent cognitive and bulbar side effects of bilateral pallidotomy, which have been confirmed in a study of 4 patients in whom contemporaneous bilateral pallidotomy was performed (91). Despite a 40% improvement in motor UPDRS scores and resolution of dyskinesias, one patient developed dysarthria, dysphagia, and eyelid opening apraxia, another developed abulia, and a third developed mental automatism. Scott et al. described hypophonia, increased salivation, and reduced verbal fluency following bilateral simultaneous pallidotomy (34). An open-label trial of bilateral simultaneous pallidotomy compared with unilateral pallidotomy plus DBS had to be halted early as all three patients with bilateral lesions developed deterioration in speech, swallowing, salivation, depression, apathy, freezing, and falling (92). In another recent series, staged bilateral pallidotomy was associated with a deficit in speech in four patients, one patient had a decline in memory, and there were three cases of infarction

(93). Further, a reduced response to levodopa has been documented in a small number of patients undergoing bilateral staged pallidotomy (93).

These results are in contrast to the milder side effects reported in one series of 14 patients who underwent staged bilateral pallidotomy, in whom no overall effect on speech and cognitive function was detected 6 months postoperatively, but in whom five had mild hypophonia, two had transient confusion, two had deterioration of gait, and one had deterioration of a preexisting dysarthria postoperatively (94). A series of 53 bilaterally operated patients was presented with a follow-up of 17 patients for 12 months (95). Major deterioration in speech (defined as a 2 point decline on the UPDRS subset score) occurred in 8% of bilaterally operated patients compared with 4% of unilaterally operated patients, although the study was not specifically designed to compare the two procedures. Similarly, postoperative major deterioration in salivation occurred in 13% and 10% of bilaterally and unilaterally operated patients, respectively. Gait freezing while on and handwriting each deteriorated with a frequency of 11% in the bilaterally operated group, and medically unresponsive eyelid opening apraxia occurred in 6%. Dysphagia was not reported. The authors suggest that these relatively low rates of complications may be attributable to the placement of a smaller lesion (100 mm^3) in the medial pallidum contributing to the lesser affected hemibody, compared with the medial pallidum contributing to the worse affected hemibody (150 mm^3). Complications were only defined according to their occurrence on the UPDRS rather than by using specific questions designed to assess their presence and severity. Additionally, precise lesion locations and cognitive results were omitted. The question of safety and timing of bilateral pallidotomy remains controversial, and this procedure has not been undertaken by many groups. It is likely to continue to fall out of favor, especially where bilateral DBS is available as an alternative.

UNILATERAL THALAMOTOMY

Vim Thalamotomy

Thalamotomy has been performed since the 1950s, when some surgeons noted the excellent relief of tremor compared to anterodorsal pallidotomy. Hassler et al. reported the successful treatment of a patient by making a lesion in the ventrolateral (VL) region of the thalamus (96), and Cooper too advocated that this was the optimal target (16). The ventrolateral region of the thalamus contains at least three important nuclei; from anterior to posterior, these are the Voa (ventral oralis anterior), Vop (ventral oralis posterior), and Vim (ventral intermediate). Hassler subsequently refined the

target to the Vop (by his nomenclature) for tremor and Voa for rigidity (97). It is now generally agreed that the optimal target for tremor control is the Vim nucleus, which receives its input primarily from the cerebellum. Although most surgeons now target Vim, in the past subthalamic sites were also targeted including the zona incerta and fields of Forel. These “subthalamotomies” were distinct from the subthalamic nucleus lesions (subthalamic nucleotomy) discussed in the next section.

The method of target selection is similar in principle to that of pallidotomy, namely that anatomical coordinates are derived from CT or MRI, and electrophysiological recording or stimulation can be used to further identify “tremor cells” and avoid the sensory nucleus (VC) and internal capsule. Lesion sizes tend to be smaller (about 60 mm³) (98) compared with pallidotomy (about 220 mm³) (27).

There have been four long-term open-label reports of thalamotomy in PD. Kelly and Gillingham reported the 10-year follow-up of 60 parkinsonian patients who had thalamotomy between 1965 and 1967 and showed sustained improvement in tremor and rigidity, but continued progression of bradykinesia (99). Later, 12 patients were reported who also had a marked improvement or cessation in contralateral tremor without complications (17). A larger series of 103 operated patients between 1964 and 1969, also followed-up for 10 years, showed that, overall, 87 patients had “good” effect, and in only 7 patients were tremor or rigidity not alleviated completely (33). Only a proportion of these patients had CT confirmation of lesion location. In a more recent series from 1984 to 1989, all 36 patients underwent CT and microelectrode-guided VL thalamotomy and 86% showed complete cessation of tremor, with the remainder showing a significant improvement up to 68 months (100). The antitremor effect was shown to be maintained in one blinded retrospective study following thalamotomy alone, subthalamotomy alone, or combined thalamotomy and subthalamotomy (101). These studies used the terminology “ventrolateral” thalamotomy.

More recently, the records of 42 patients with PD who underwent thalamotomy were reviewed, and 86% had cessation of or moderate-to-marked improvement in their contralateral tremor, with a concomitant improvement in function which persisted for as long as 13 years. The mean daily dose of levodopa was reduced by 156 mg and lesion location was in the Vim (102). Postoperatively, rigidity improved by 30%, ipsilateral tremor worsened, and there was no significant change in other features of parkinsonism.

The complication rates of unilateral thalamotomy range from 10% transient confusion and 8% facial weakness or numbness (33), to 58% transient and 23% persistent complications of contralateral weakness,

dysarthria, and blepharospasm (18). Twenty-two of the 36 (61%) in the series of Fox et al. experienced complications. Half of these cleared by 7 days and only 6% were permanent or bothersome, including dysarthria, dyspraxia, or cognitive dysfunction (100). Deficits of verbal memory are more common after left thalamotomy compared with right thalamotomy (103).

One study compared the short-term safety and efficacy of Vim thalamotomy with Vim stimulation (104). Cessation or improved tremor resolution was detected in 79% of the lesioned group compared with 90% in the stimulated group. These results were not statistically different, but only 18% of the lesioned group had an improved functional status compared with 55% of the stimulated group. Additionally, the complication rate for the stimulated group was 16% compared with 47% in the lesioned group, but there was one death in the stimulated group. These positive and negative effects of thalamotomy and thalamic DBS are very similar to a retrospective report comparing the two treatments (105), in which it was additionally shown that tremor recurrence occurred in 15% of patients with thalamotomy, but only in 5% of patients with DBS. Consequently, 15% of patients with thalamotomy required reoperation. These studies show the expected improved morbidity of DBS compared with irreversible lesioning. However, long-term follow-up (up to 40 months) has highlighted the potential hardware complications of DBS, which include lead fracture, erosion or migration, infection, cerebral spinal fluid (CSF) leak, short or open circuits, or other system malfunctions (106). In one study the mean time to the first complication was 10 months (107). From these studies it is estimated that 25–40% of patients with deep brain stimulators may require further surgery to maintain good clinical outcome (106–108). Further long-term comparative studies are necessary to define whether the potential short-term reduction of side effects of DBS outweighs the higher long-term need for re-operation as a result of hardware failure.

The Vim nucleus is proposed to be the cerebellar recipient nucleus of the thalamus, and so the effect on tremor may have a different physiological basis from the improvement of bradykinesia and dyskinesia that accompany internal pallidotomy. It is proposed that internal pallidotomy affects the thalamic nuclei that receive inputs from the basal ganglia (Voa and Vop). One factor that therefore continues to confound our understanding of thalamotomy is the variability of lesion locations across series. This is more problematic than with pallidotomy since the boundaries of the thalamic nuclei are not as well demarcated anatomically as in the pallidal complex and the nomenclature of the thalamic nuclei varies across series and also from human to primate (Figs. 4, 5).

The above studies support a role for Vim thalamotomy in patients whose predominant symptom is medically intractable asymmetrical tremor

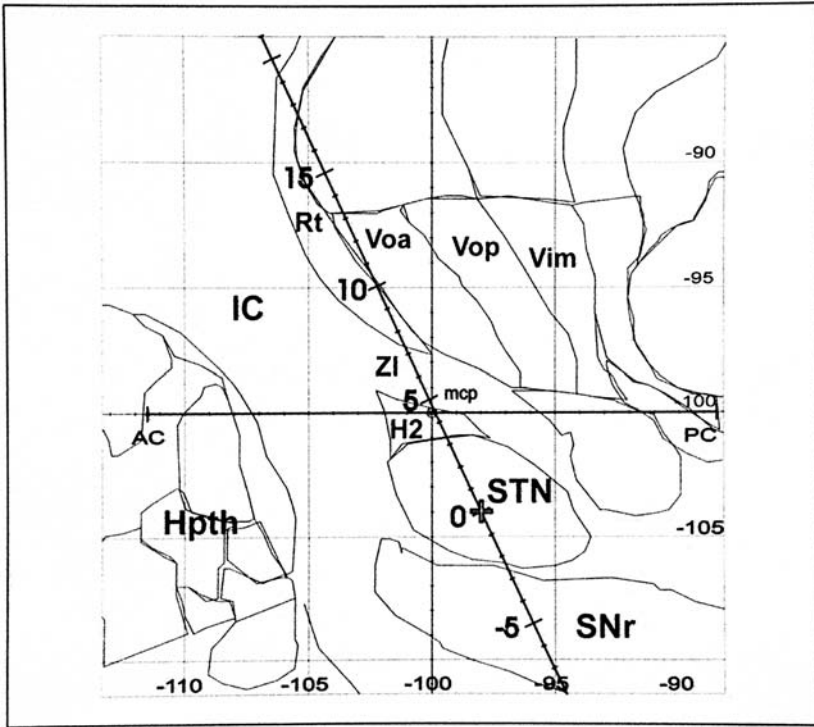


FIGURE 4 Stereotactic trajectory targeting the subthalamic nucleus (STN) and showing the relative positions of the thalamic nuclei Voa, Vop and Vim, the Zona incerta (ZI), the substantia nigra (SNr) and the commissural plane. AC = anterior commissure, PC = posterior commissure, mcp = mid commissural point, Hpth = hypothalamus, IC = internal capsule. (From Ref. 125.)

and who are not suitable for DBS. The majority of patients with PD are, however, likely to have progressive bradykinesia, even if this is not present at the time of presentation for surgery. This symptom is not modified by Vim thalamotomy, and so thalamotomy (and Vim DBS) in the treatment of PD has largely been replaced by alternative therapies.

Thalamic Targets Other Than Vim

It would not be predicted from the known anatomical circuits that Vim thalamotomy would improve dyskinesia, and yet there are reports of this. Five patients in the series of Jankovic et al. had considerable improvement in levodopa-induced dyskinesia following Vim thalamotomy (18). The location of these antidyskinetic lesions may not have been confined to Vim

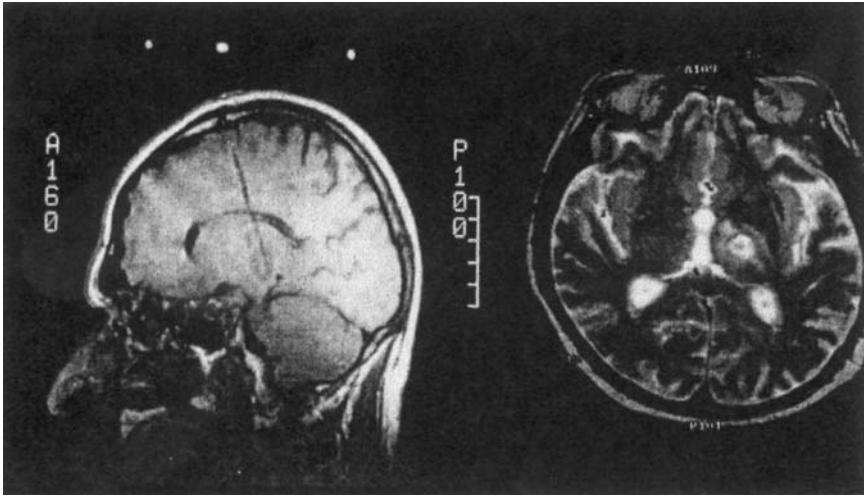


FIGURE 5 MRI scan of unilateral Vim thalamotomy. (Courtesy of Dr. A. M. Lozano, Toronto Western Hospital, Ontario, Canada.)

and may have included more anterior regions in ventrolateral thalamus. One patient in the series of Fox et al. had improved levodopa-induced dyskinesia following ventrolateral thalamotomy (100). The antidyskinetic findings have also been replicated in experimental monkeys in which thalamotomy was stereotaxically tailored to the thalamic nuclei that receive afferents from the internal pallidum (109) and shown to abolish contralateral chorea but not dystonia. Interestingly, Vim thalamotomy did not affect these dyskinesias and thalamotomy encroaching on the centromedian nuclei reduced, but did not abolish, chorea.

These findings have been reproduced in humans (110). In an older series, Vim thalamotomy was performed via one needle tract, and another lesion was deliberately placed more anteriorly via another needle tract in the Voa/Vop complex specifically to relieve rigidity. Patients in whom the Voa/Vop region was also targeted had almost complete resolution of contralateral dyskinesia as well as tremor, and those whose lesions were restricted to Vim did not experience a reduction in dyskinesia (111). Recently there has been a retrospective correlation of the location of the tip of thalamic deep brain stimulators (stereotaxically aimed at the Vim) with clinical outcome. It was shown that electrode tips placed more medially and ventrally were more likely to be associated with the resolution of levodopa-induced dyskinesia (112). It was concluded that these electrode tips lay

within the centromedian (CM) and parafascicular (PF) thalamic nucleus and not in the Vim. Interestingly, however, they were equally effective in the resolution of tremor. It has been suggested that CM/PF thalamic stimulation may lead to reduction of dyskinesia by reducing internal pallidal input to these nuclei, in contrast to Vim stimulation, which interrupts the cerebellar-thalamic circuits. These findings are, however, at odds with a single case report of a CM/PF thalamotomy, which was inadvertently placed during an attempt to treat a tremulous patient with PD with DBS of the Vim (113). Postoperatively, this patient had suboptimal contralateral tremor control and a progressive worsening of contralateral parkinsonism. The patient died from an unrelated illness 12 years later, with exhausting dyskinesia present. Postmortem examination showed that one of the electrode tracts was associated with a cavity within the CM/PF nucleus, which was marginally larger than the volume of the electrode tip, but the entire surrounding CM/PF nucleus showed marked astrocytosis and neuronal loss. There has not been a direct comparison of the positive and negative effects of lesions of different thalamic nuclei, nor of ventrolateral thalamotomy with internal pallidotomy. Further clinical trials with precise imaging of Vim, Voa, Vop, VL, CM, and PF thalamotomy would, therefore, be required before clinical-pathological correlations can be made reliably.

BILATERAL THALAMOTOMY

The clinical efficacy of bilateral thalamotomy in terms of resolution of bilateral tremor is as effective as unilateral thalamotomy for unilateral tremor (102). However, a high incidence of speech disturbance has been noted in several series: 18% (33), 44%, (32), and 60% (114). The high rate of speech and cognitive deficits following bilateral thalamic lesions has persuaded most surgeons to offer patients an alternative to bilateral thalamotomy if bilateral surgical treatment is required.

UNILATERAL SUBTHALAMIC NUCLEOTOMY

The realization that the neurons of the subthalamic nucleus (STN) in parkinsonian monkeys are overactive led to interest in this nucleus as a possible target for therapy for PD (115). It is postulated that overactivity of the STN leads to excessive excitatory drive to the medial pallidum. The occurrence of cognitive deficits reported with thalamotomy and pallidotomy has driven the interest in trying to find alternative targets to lesion, especially for patients who require bilateral procedures and who are not suitable for DBS. The most recent development in lesion surgery is the

reevaluation of “subthalamotomy.” Surgeons previously avoided the STN given the longstanding awareness that lesions of the normal STN in normal primates can have a deleterious effect by causing hemiballism (116), and this is a well-known consequence of infarcts and hemorrhages in this region in humans. In contrast, it has been shown that excitotoxic (117) or thermocoagulation (118) lesions of the pathological STN in MPTP-treated primates can alleviate parkinsonism. It should be realized that these thermocoagulation lesions involved the internal capsule, ansa lenticularis, and globus pallidus (118,119), and so the clinical benefit in these cases may not have been solely due to deactivation of the STN.

Early studies of deactivation of the subthalamic area by lesioning cannot be used to provide good quality evidence by today’s standards because the lesions in this eloquent region of the brain were not anatomically well defined (120). Indeed, as mentioned above, “subthalamic” lesions usually purposefully avoided the STN proper in an attempt to prevent hemiballism. When the STN became a logical target in the surgical treatment of PD, concern over the possibility of introducing chorea led neurosurgeons to apply DBS rather than electrocoagulation to this site, since the former can be successful and yet is more reversible (39,121). However, the relatively high technological demands and costs of DBS have recently encouraged some groups to attempt subthalamic nucleotomy in patients with PD. Data on the safety and efficacy of this approach are very limited.

There have been only three open-label, nonrandomized reports of the use of unilateral subthalamic nucleotomy in PD. The target in one study was the sensorimotor region of the dorsal STN, defined by semimicrorecordings and stimulation (20). These authors showed a sustained reduction in off motor UPDRS by 50% in 10 of 11 patients, and this effect was maintained in 4 of 11 patients for 2 years. UPDRS on scores and ADL scores also improved “drastically.” Ipsilateral bradykinesia improved by 20%, but this effect was not sustained at 12 months. Axial scores for gait and postural instability showed marked and sustained improvements. Dyskinesias were seen in the contralateral limbs of 5 patients during lesioning and lasted up to 12 hours before abating spontaneously. One patient developed transient delayed chorea. Another patient developed a post-operative infarction affecting the area of the lesioned STN, zona incerta, and ventral thalamus. This resulted in severe contralateral dyskinesia that persisted despite cessation of all levodopa and eventually required treatment with a pallidotomy on the same side as the “subthalamotomy.” It is interesting to note that, apart from this patient, the dose of medication was maintained for 12 months, unlike cases of bilateral subthalamic DBS in which medication doses can be reduced significantly.

In the second series, the target was the central area of the subthalamus in nine patients and lesioning was guided by macrostimulation (21). Efficacy results were not reported, but only one patient developed chorea post-operatively, which initially required medical treatment but then subsided spontaneously to only mild movements. Four subjects had their medication doses reduced. In the series of Gill and Heywood, five patients had unilateral and five had bilateral small subthalamotomies with improved parkinsonism, and only one case had mild dyskinesia (122). These early studies showed that the risk of significant chorea after unilateral “subthalamotomy” is about 10% and that medication doses may not be significantly reduced, possibly because the ipsilateral side is minimally affected by the lesion.

The precise location of lesions in the subthalamic area needs further confirmation of exactly where the optimal target should be placed. It could be hypothesized, for example, that discrete small lesions confined to the nucleus (i.e., subthalamic nucleotomy) may be more likely to lead to chorea, whereas lesions that include the subthalamic nucleus but also extend dorsally (i.e., subthalamic nucleotomy with additional interruption of the ansa lenticularis, zona incerta, lenticular fasciculus) may be less likely to induce chorea since any potential to induce chorea may be counteracted by the concurrent interruption of these efferent fibers from the internal pallidum. However, the experience of Alvarez et al. (20), in which the one patient with the large infarct involving the more extensive area had the most severe persistent hemiballism, suggests that this prediction may not be correct. Therefore, the exact location and role of unilateral lesions of the subthalamic region remains unclear in clinical practice.

BILATERAL “SUBTHALAMOTOMY”

The effects of bilateral subthalamic nucleotomy were reported earlier than unilateral “subthalamotomy.” There has only been one report of two patients dedicated to this subject, showing that small lesions in the dorsolateral STN could reduce the off motor UPDRS scores by over 68% without inducing dyskinesia (123). Both patients were reported to have no complications and to have medication withdrawn. This group later reported in abstract that bilateral “subthalamotomy” had been accomplished safely in five subjects (122). There is one other report of a stereotaxic “subthalamotomy” performed for dystonia, which was associated with bilateral apraxia of eyelid opening (124). It is premature to comment on the place of such surgery in clinical practice.

CONCLUSION

The single most consistent result of unilateral pallidotomy is the resolution of contralateral dyskinesia, and this therapy is best reserved for those few patients who exhibit asymmetrical disabling dyskinesia when on medication and whose level of parkinsonism is unacceptable when the medication is reduced. In general, the thalamic target has been largely abandoned in the surgical management of PD. Unilateral thalamotomy could be considered for those few patients who exhibit asymmetrical longstanding tremor that is unresponsive to maximum tolerated doses of medication and who have few or nonprogressive signs of parkinsonism, or for patients who have required multiple battery changes following unilateral stimulation of the ventral intermediate nucleus. These groups comprise only a small minority of patients with advanced PD in whom the signs are typically bilateral and progressive. In this situation, the optimal therapy at the moment is bilateral DBS of the STN or internal pallidum, although the STN is generally favored. Bilateral pallidotomy and thalamotomy are rarely performed due to concerns about postoperative speech and cognitive decline. The role of unilateral and bilateral lesions of the subthalamic region remains to be established. Few data are available on long-term follow-up. Lesion site, size, the inclusion of external pallidum, ansa lenticularis, Voa/Vop, STN, peri-STN structures, the need for microelectrode recordings, and the safety and efficacy of bilateral lesions all remain important and controversial issues in lesion surgeries.

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