Surgical Treatment of Parkinson Disease

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SEVERAL EFFECTIVE NEUROSURGICAL treatments for Parkinson disease (PD) have been developed based on an improved understanding of basal ganglia circuitry and the continuing evolution of neurosurgical techniques. Currently, there are 3 surgical targets for the treatment of movement disorders, the globus pallidus interna (Gpi), the subthalamic nucleus (STN), and the Ventralis intermedius nucleus of the thalamus. The Gpi and the STN are the preferred targets for the treatment of PD while Ventralis intermedius is now primarily targeted in the treatment of tremor. Options for treatment include the placement of a deep brain stimulating (DBS) electrode in any of these areas or the creation of a small lesion in the Gpi (pallidotomy) or in the thalamus (thalamotomy).

Surgery for Treatment of PD

Thalamotomy was introduced in the 1950s and was found to relieve tremor and rigidity, though bradykinesia was generally unaffected.[1] During the same era, pallidotomy was found to significantly improve tremor, rigidity, and bradykinesia.[2] This early period of neurosurgical treatment for PD came to an end with the introduction of dopamine (levodopa) replacement therapy in the late 1960s. Since then, it has become clear that dopamine replacement is not a cure for PD. After 5 to 10 years of medical treatment, the disease becomes increasingly difficult to manage, balancing control of PD symptoms with adverse effects of the medications. At this point in the patient's disease process, surgical therapy may be considered.

Contemporary neurosurgical practice is based on the premise that the Gpi and the STN are overactive in PD.[3] The goal of surgery is to precisely localize the target nuclei and to reduce the excessive output.[4-6] There are 2 techniques for reducing activity, ablation and DBS. Ablation entails creating a small lesion by inserting an electrode into the target nucleus and heating the tip to 65°C to 85°C.[7] The result is a small area of necrosis around the tip of the electrode.[8] Deep brain stimulation involves the placement of an implanted electrode in the target nucleus. The basis of this approach is the empiric intraoperative observation that high-frequency stimulation in a particular nucleus leads to a functional effect similar to the creation of a lesion.[4] For example, high-frequency stimulation of the Ventralis intermedius nucleus of the thalamus leads to a reduction in tremor similar to that observed after creating a lesion.[9] A small number of experimental studies have suggested that high-frequency stimulation of the Gpi or the STN leads to inhibition of the surrounding neurons.[10-12] The mechanism of action is still unclear but may be due to the release of γ-amino butyric acid from afferent terminals or to a type of depolarization blockade.[10,11]

Indications for Surgery. Patients considered for surgery should have disabling idiopathic PD with a documented response to dopamine replacement therapy. Candidates should be evaluated by an experienced movement disorders team to ensure that medical treatment has been optimized. It is important to determine the major source of the patient's disability so that realistic goals can be agreed upon prior to surgery. Contraindications to surgery include the PD-plus syndromes, such as progressive supranuclear palsy and multisystem atrophy. These disorders are characterized by neuronal loss in multiple areas; therefore, standard neurosurgical procedures are often ineffective and may lead to further decline. Other contraindications include dementia or serious systemic illness.

Surgical Technique. The main features of the surgical technique are similar for all targets. The surgical target is identified using stereotactic magnetic resonance imaging and/or computed tomography prior to surgery.[13] The patient is then brought into the operating room and the procedure is performed with the patient awake. Using local anesthesia, a burr hole is created that allows the introduction of recording, lesioning, and stimulating electrodes. Most centers use microelectrode recordings to precisely determine the location of the nuclei.[5,6] Stimulation can also be used to delineate the target location.[7] Once physiologic confirmation is completed, the lesion is generated or the DBS electrode is placed (FIGURE). If a stimulator is inserted, the patient receives general anesthesia after confirmation of the brain electrode placement, to allow infraclavicular pulse generator implantation. Currently, DBS is approved by the Food and Drug Administration for use in the thalamus but is used in the Gpi or the STN as an off-label indication. Food and Drug Administration approval for these other sites is expected in the near future.

Thalamotomy and Thalamic Stimulation. Candidates for thalamotomy or

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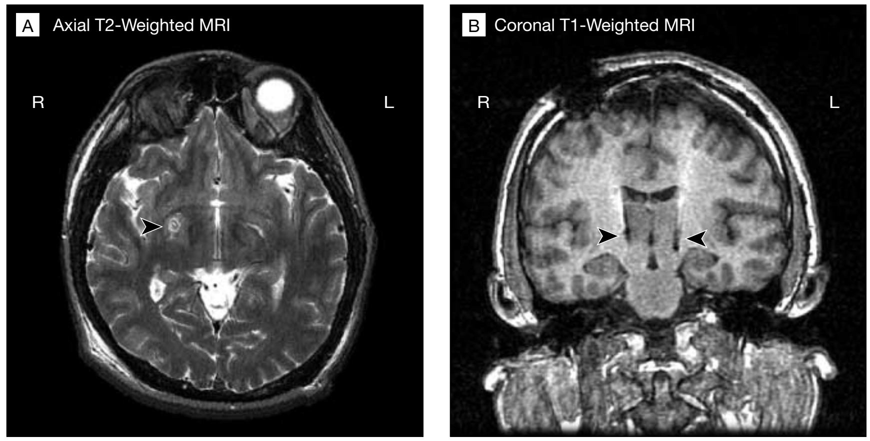
thalamic stimulation should have tremor refractory to medical therapy, representing the predominant form of disability. Patients with PD who have other motor signs should be considered for surgery aimed at other targets, such as the Gpi or the STN.

Thalamotomy is an effective treatment for patients with unilateral or asymmetric PD in which tremor predominates. In a study of the long-term effects of unilateral thalamotomy on 60 patients, contralateral tremor was abolished in 90% of patients at the first postoperative evaluation.[14] Subsequent evaluations revealed that the effect diminished somewhat over time. The results of thalamic stimulation are largely comparable with those of thalamotomy. Patients with tremor-predominant PD have a sustained response rate of 80% to 95%.[15] In a recent randomized study, the effects of both techniques were similar, though patients with thalamic stimulators reported having a better functional outcome at 1 year follow-up.[16]

Figure. Magnetic Resonance Images (MRIs) Showing Placement of Deep Brain Stimulating Electrodes



A, Axial T2-weighted MRI following a right-sided pallidotomy. The lesion (black arrowhead) is in the posterior ventral globus pallidus. B, Coronal T1-weighted MRI following placement of bilateral deep brain subthalamic stimulators (black arrowheads). The electrode has 4 1.5-mm contacts separated by 0.5 mm. The leads can be activated singly or in combination as necessary to stimulate the subthalamic nucleus while avoiding other structures.

Pallidotomy and Pallidal Stimulation. The modern era began in the early 1990s when pallidotomy was successfully reintroduced for management of refractory PD.[17] Following the initial reports, many centers adopted pallidotomy with apparently comparable degrees of efficacy.[7,18-33] Unfortunately, most studies are uncontrolled case series and not all studies used uniform outcome measures.[34] The standard outcome measure is the Unified Parkinson Disease Rating Scale (UPDRS), which has 4 parts: mentation, activities of daily living, motor, and complications. The patients are assessed while taking their medications and during a defined off period without medications. A recent review of contemporary pallidotomy literature identified a total of 85 articles with 1735 patients who underwent a unilateral pallidotomy.[35] Of these, 501 and 218 patients had documented UPDRS scores at 6 and 12 months, respectively. There was a consensus on the benefits of pallidotomy. Pallidotomy resulted in an average of 45% improvement in off-state motor symptoms, including tremor, rigidity, and bradykinesia. The primary benefit of pallidotomy during the on state is a dramatic reduction in contralateral dyskinesias by 80% to 90%. In addition, most patients experience a decrease in the severity of on/off fluctuations. Although few long-term studies are available, it appears that the effects of pallidotomy are relatively durable, with most patients retaining at least some benefit at 2 years postoperatively and, in at least 1 report, for up to 5 years.[36-38] On-period scores and mentation scores are generally not affected. In the aggregate, these benefits result in marked functional improvement for most patients. Bilateral pallidotomy has been used in a smaller number of patients with apparently good results, though there is a higher rate of complication.[39] The role of DBS in the Gpi is less well established but the results appear similar to pallidotomy results.[40-44] The Gpi-DBS has the advantage that it can be used bilaterally. In a recent study of 38 patients with bilateral Gpi-DBS evaluated in a double-blind fashion, there was an average 37% improvement in UPDRS motor scores, a 67% reduction in dyskinesias, and relatively few complications.[44]

Subthalamic Stimulation. In comparison with the Gpi and the thalamus, the STN has only recently become the target of neurosurgical procedures. Experimental studies in parkinsonian animals demonstrated that lesions in the STN lead to significant improvements.[45] Most centers were reluctant to lesion the STN for fear of causing hemiballismus (uncontrolled flinging movements contralateral to the lesion), though a few centers have performed subthalamotomy.[46] This difficulty has been overcome by the use of DBS electrodes.[4,42,44,46-53] Since the amplitude of the stimulation is adjustable, it is possible to titrate the effect below the level causing hemiballismus.

There are still relatively few published studies regarding DBS in the STN (TABLE).[42,44,46-53] In a study of 24 patients implanted with bilateral stimulators, off-period activities of daily living and motor scores were improved by 60% at 1 year.[47] Dyskinesias were not directly reduced by the procedure but the mean dose of dopamine was reduced by 50% leading to a significant decrease in on-period dyskinesias. In a recent multicenter study of bilateral DBS of the STN using a double-blind evaluation of 96 patients, UPDRS motor scores improved by 49%, dyskinesias were reduced by 58%, and the mean dose of levodopa was decreased by

Table. Comparison of 6- and 12-Month Outcomes Following Pallidotomy and Bilateral Subthalamic Stimulation*

	Pallidotomy[35]		STN Stimulation[44,46-53]	
	6 mo	12 mo	6 mo	12-36 mo
No. of patients	256	161	154	60
UPDRS part 3 off medication improvement, %	40.6	45.3	55.7	60.2
Reduction in levodopa, %	NA	NA	48.6	51.3

*UPDRS indicates Unified Parkinson Disease Rating Scale; STN, subthalamic nucleus. The STN stimulation data are derived from available studies and represent a weighted average of the number of patients in each study. NA indicates not applicable because the pallidotomy study reported either no change in dopamine dosage or no data were given. Patients in pallidotomy study are only those with adequate UPDRS scores reported.

37%.[44] In general, there is either little or no change in scores of the on-period or in the mentation portion of the examination.[44,46-51] Bilateral STN stimulation appears to be relatively well tolerated, though patients older than 69 years may be at higher risk for cognitive dysfunction.[54] There is little tissue damage around a chronically implanted electrode.[55] Subthalamic stimulation is usually performed bilaterally in part because patients who are treated unilaterally may experience excessive dyskinesias if they are maintained on the same dopaminergic medication dosage. Conversely, if the medications are reduced, then the unoperated side becomes undertreated.

Transplantation

Parkinson disease has long been an attractive target for transplantation therapy because there is loss of a discrete population of neurons and the circuitry is relatively well understood. A number of approaches have been tried including adrenal medullary grafts, porcine xenografts, and embryonic dopamine neuron transplants.[56-59] In practice, it has been difficult to achieve results that are comparable with those achieved by either pallidotomy or DBS. Adrenal grafts are largely ineffective.[34] Porcine xenografts offer a smaller clinical benefit than standard surgical techniques and have problems related to their immunogenicity. In the only well-controlled trial of embryonic dopamine neuron transplants, there was a 34% improvement in motor scores in younger patients (no improvements in motor scores in older patients) and 15% of patients developed intractable dyskinesias.[59] While these results are promising in some respects, it is clear that more refinement is needed before transplantation is widely adopted. Stem cell transplants appear to have potential but remain experimental.[60]

Conclusions

Thalamotomy and thalamic stimulation have only a small role in current PD management because instrumentation of the Gpi and the STN provides better control of symptoms other than tremor.[34] Even patients whose primary complaint is tremor may be expected to progress and develop other symptoms of PD with time.

During the 1990s, most centers performed pallidotomies. Recently, many centers have switched to an almost complete reliance on subthalamic stimulation or pallidal stimulation. Pallidotomy is a proven and apparently durable treatment but involves creating a permanent lesion. If the lesion is incorrectly placed, it may result in little or no benefit and may cause adverse effects, such as visual field defects, though such complications are rare in experienced centers. Pallidotomy does have the advantage of being a single procedure. A well-placed lesion results in significant benefit; patients have no implanted hardware and do not need stimulator adjustments. The Gpi stimulation is relatively comparable with pallidotomy and may be used bilaterally.

Although the overall benefits of subthalamic stimulation appear to be comparable with those of pallidotomy or pallidal stimulation, the technique has become attractive for several theoretical reasons. One of the advantages is that STN stimulators can be placed bilaterally, at least in younger patients, whereas bilateral pallidotomy has not been widely used. The idea of using a reversible and adjustable stimulator is inherently appealing. The observation that patients with bilateral STN stimulators can reduce their medications is also appealing since the medications can cause adverse effects. An additional theoretical advantage of the technique is that it may reduce STN-mediated excitotoxic damage to dopaminergic neurons in the substantia nigra, an idea that has some support in animal studies.[61] Although not yet demonstrated in humans, this theory suggests that treating younger patients with subthalamic stimulation may slow disease progression. Subthalamic nucleus DBS has its own disadvantages. The surgery is more complex and patients need frequent stimulator adjustments afterward. In addition, there are risks associated with implanted hardware such as migration, malfunction, breakage, and infection along with the necessity of changing batteries every few years. A final consideration is the added cost of the stimulator hardware.

At present, it is difficult to unequivocally recommend one technique over the others. A number of factors must be considered including patient age, primary source of disability, and the patient's wishes. In general, pallidal stimulation might be preferable for patients who suffer from dyskinesia as the major source of disability and pallidotomy might be appropriate in cases where frequent stimulator adjustments are impractical. The STN stimulation may be more suitable for patients with significant disability off medications and in younger patients in whom it may be desirable to maintain intact circuitry so that newer treatments may be used as they become available.

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