UPDATE ARTICLE

Surgical Treatment For Parkinson's Disease

G K K Leung,* MBBS, BSc, FRCS
K N Hung, MBBS, FRCS, FHKAM
Y W Fan, MBBS, FRCS, FRACS, FHKAM
Department of Neurosurgery
Queen Mary Hospital

Summary

Advances in stereotactic and functional neurosurgical techniques have brought about new developments in the surgical treatment for Parkinson's disease, including methods such as ablative therapy, chronic brain stimulation, stereotactic radiosurgery and transplantation. Significant benefits can be provided for patients who have become refractory to medical therapy or developed adverse side-effects after prolonged administration of levodopa. (*HK Pract* 1999;21:106-115)

摘要

隨著立體定位和功能性神經外科技術的發展，出現不少治療帕金氏病的新方法，包括熱融切除術、持續大腦刺激法、立體定位放射治療及移植手術等等。對因長期服藥而產生頑強抗藥性或副作用的患者有明顯療效。

Introduction

Parkinson's disease (PD) is a common neurological problem. The local prevalence of PD is unknown. Although it has been estimated that around 2,500 patients are affected in Hong Kong, the actual figure is likely to be considerably higher.[1] At present, there is no cure for PD and its treatments aim at symptomatic relief. Surgical treatment for PD was first developed in 1950's but it fell out of favour with the introduction of levodopa in 1960's. It was soon realized, however, that although levodopa is the most efficacious form of treatment, it is not the permanent answer to PD. As the disease progresses and with prolonged levodopa administration, symptoms become refractory to the drug. Patients require an increasing dosage while being at risks of developing abrupt "on-off" episodes and disabling side-effects such as dyskinesia (involuntary movements). With advance in stereotactic and functional neurosurgical techniques, there has been resurgent interest and rapid developments in the surgical treatment for PD over the last two decades.

The aim of surgery is to improve function by abolishing the symptoms (e.g. tremor, bradykinesia, rigidity) without incurring added neurological deficit. Patient selection and the

* *Address for correspondence :* *Dr G K K Leung, Medical Officer, Department of Neurosurgery, Queen Mary Hospital, Hong Kong.*

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choice of procedure are of paramount importance in determining treatment success. In general, surgery is indicated if the symptoms are disabling and persistent after adequate trial with medical therapy. Medical therapy and surgical treatment, however, are by no means mutually exclusive. Indeed, previously effective control by levodopa may indicate good response to surgery and many patients continue to require some form of drug treatments after surgery, albeit post-operative reduction in dosage requirement and drug-related side-effects, and improvement in PD symptoms. Major contraindications to surgery include dementia, uncontrolled hypertension, bleeding disorders, and "atypical" parkinsonian syndromes, which do not respond well to surgery. Old age is not a contraindication per se but is associated with increased surgical risks. **Table 1** lists the available surgical methods for the treatment of PD. A multidisciplinary approach is essential and involves contribution from the neurosurgeon, neurologist, neuroradiologist, neurophysiologist, neuropsychologist and a rehabilitation team.

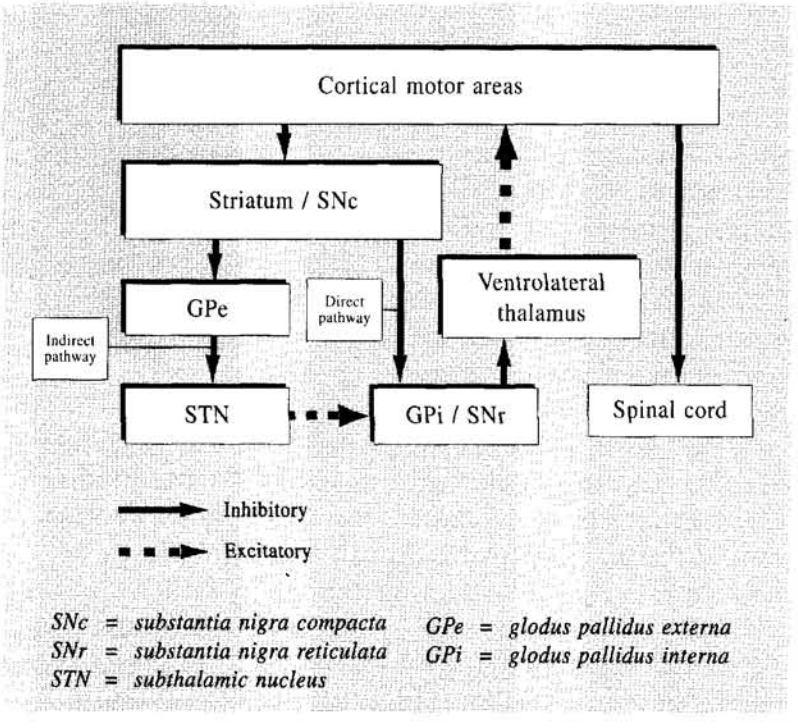
Pathophysiology

Although the pathogenesis of most movement disorders is poorly understood, it is now widely accepted that PD results from the loss of dopaminergic neurones and subsequent dysfunction within the basal ganglion, which is responsible for the initiation, maintenance, and modulation of voluntary movement. **Figure 1** gives a modified schematic representation of the basal ganglia-thalamocortical motor circuit. The latter is essentially a re-entrant pathway through which signals from the motor cortex (e.g. 'to move') are processed within the basal ganglion and thalamus, and then returned to the motor cortex. The striatum, composed of the caudate nucleus and the putamen, receives input from the motor cortex. The globus pallidus interna (GPi) and substantia nigra reticulata (SNr) complex acts as the output station of the basal ganglion. The 'direct' and 'indirect' pathways function respectively as positive and negative feed-back loops which regulate the thalamocortical activities. In PD, reduction in dopaminergic activities results in loss of inhibition from the 'direct' pathway and increased stimulation

Table 1: Surgical methods for the treatment of Parkinson's disease

Ablative therapy	– Thalamotomy
	– Pallidotomy
Chronic deep brain stimulation	– Thalamic stimulation
	– Pallidal stimulation
	– Subthalamic nucleus stimulation
Stereotactic radiosurgery	
Transplantation	

Figure 1: A modified schematic representation of the basal ganglia-thalamocortical motor circuit



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from the 'indirect' pathway to the GPi/SNr complex. The net effect is increased inhibition from GPi/SNr to the thalamocortical pathway, causing the classic hypokinetic symptoms of akinesia (poverty of movement), bradykinesia (slowness of movement) and rigidity (lead-pipe or cog-wheel types) seen in PD. Conversely, hyperkinetic symptoms such as levodopa-induced dyskinesia may arise from reduced inhibition from the GPi/SNr complex.[2] Interestingly, both hyperkinetic and hypokinetic symptoms can coexist clinically, indicating that more complex mechanism is at work. The mechanism of tremor-production is controversial but is probably associated with 'tremor-producing' cells within the thalamus.

Ablative therapy

Principles and techniques

The strategy of ablative therapy involves the use of stereotactic technique and selective deep brain lesioning to release the motor circuit from abnormal activities described above.[3] A stereotactic head frame is first mounted onto the patient's skull under local anaesthetics. (**Figure 2**) Imaging studies, using magnetic resonance imaging (MRI) and computerized tomography (CT), are then carried out with the head frame in-situ. The anterior and posterior commissure (AC-PC) line, which runs along the longitudinal axis of the third ventricle, acts as the most important reference landmark, and with the aid of computer software and brain atlas, the appropriate target can be localized in Cartesian (x,y,z) co-ordinates with respect to the head frame. (**Figure 3**) The patient is then transferred to the operating room, where, under local anaesthesia, a burr hole is made in the patient's skull through which a recording/stimulation electrode can be inserted towards the intended target under the guidance of the stereotactic frame.

Figure 2: A stereotactic frame is mounted onto the patient's skull with pins

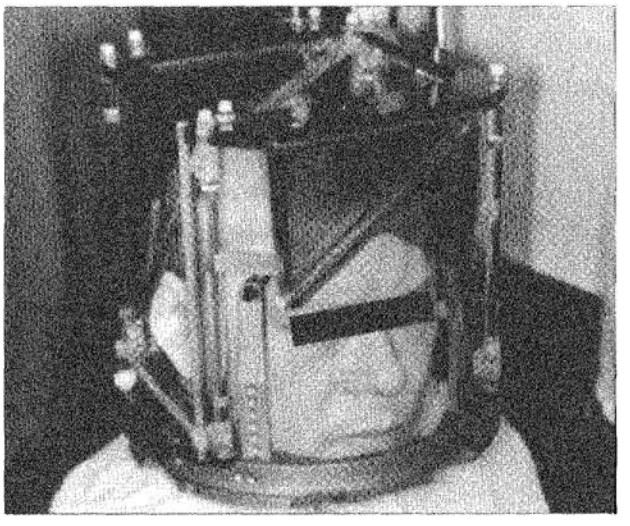
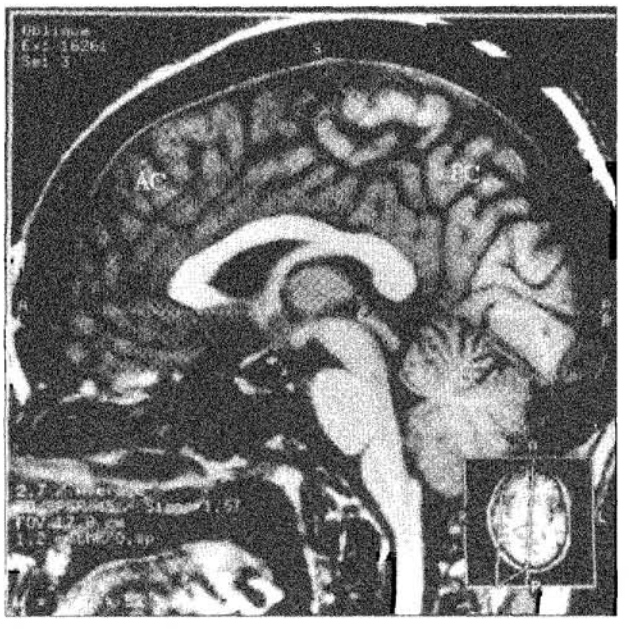


Figure 3: Mid-sagittal MRI image (T1-weighted) showing the anterior commissure-posterior commissure (AC-PC) line



Target localization is confirmed and refined using electrophysiological methods. (**Figure 4**) For example, an electrode tip placed within the ventralis caudalis (Vc) nucleus of the ventrolateral thalamus

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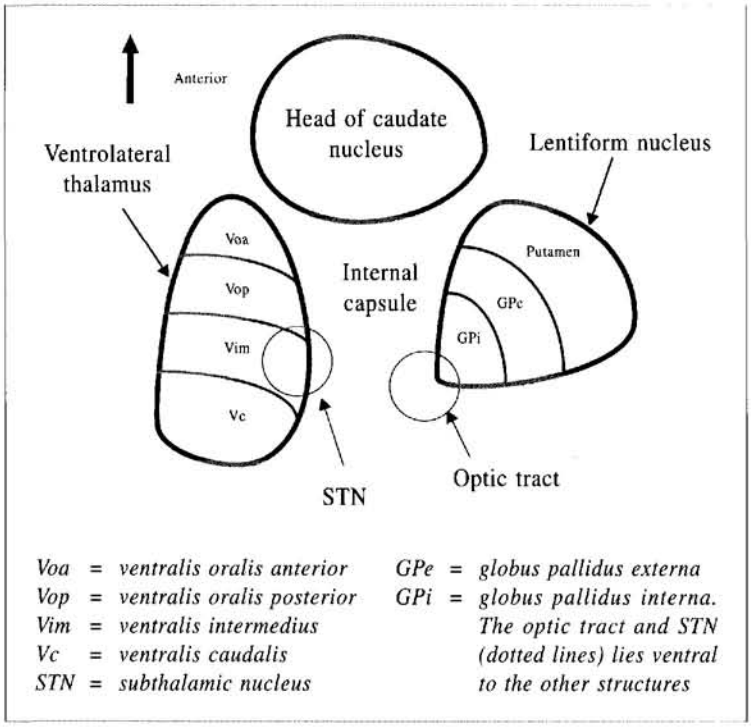
will record activities in response to contralateral fine touch stimuli, whereas within the ventralis intermedius (Vim) nucleus, tremor frequency discharges or response to contralateral proprioceptive stimuli can be observed. When stimulation is applied, a correctly placed electrode within the Vim will either drive or abolish tremor, depending on the stimulating frequency, whereas stimulation within or near the internal capsule will result in movements of the contralateral limbs.[4] As the patient remains awake throughout the procedure, the surgeon can check for therapeutic effects (e.g. tremor arrest) as well as unwanted side-effects (e.g. dysarthria, paraesthesia) during test stimulation. The aim is not only to locate the best lesioning target for the maximal clinical benefit but also to ensure that nearby structures with crucial functions are not damaged.

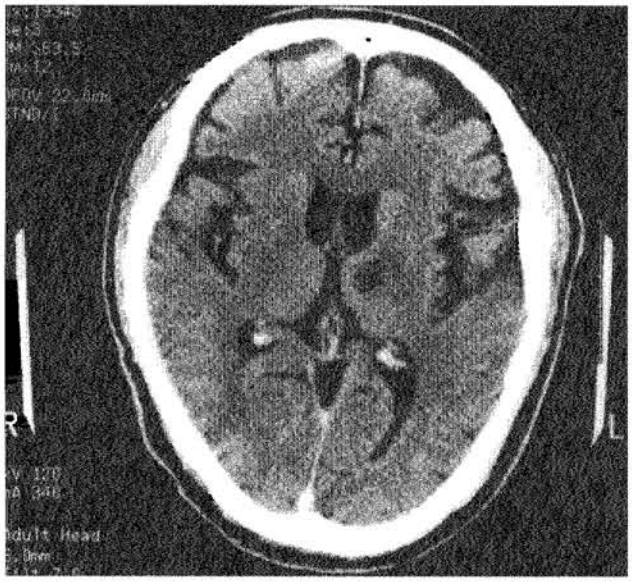
Once the target is confirmed, ablation is achieved with the use of radiofrequency (RF) lesioning technique. With a specially designed RF generator, the appropriate choice of probe, lesioning temperature and duration, a lesion of highly controlled size and shape can be made. (**Figure 5**) A test lesion is made first. If the effects are desirable, a permanent lesion is then made, repeatedly if necessary. Irreversible neuronal ablation usually occurs with a lesioning temperature of 75°C for 60 to 90 seconds. After the procedure, the patient initially resumes the pre-operative medications and can be discharged within a few days.[5] Diligent and long-term follow-up is essential, ideally by the same multidisciplinary team mentioned above.

Figure 4: Structures of the right ventrolateral thalamus and basal ganglion in axial cross-section seen from above



Voa = *ventralis oralis anterior*
Vop = *ventralis oralis posterior*
Vim = *ventralis intermedius*
Vc = *ventralis caudalis*
STN = *subthalamic nucleus*
GPe = *globus pallidus externa*
GPi = *globus pallidus interna.*
The optic tract and STN (dotted lines) lies ventral to the other structures

Figure 5: Post-operative axial CT image showing a left thalamotomy lesion



Thalamotomy

The lesioning target in thalamotomy is the ventralis intermedius (Vim) nucleus of the ventrolateral thalamus. Thalamotomy can improve contralateral tremor in 86% of PD patients. Rigidity and bradykinesia in general respond poorly.[6] Most

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patients experience significant functional improvement although the effect may decrease with time due to disease progres-sion.[7] General mortality (0.5 to 1%) and morbidity (2-5%) is low. Specific complications include contralateral paraesthesia and weakness due to damages to the Vc or internal capsule respectively. Dysarthria and memory deficit may be transient or permanent. Damage to the subthalamic nucleus may result in hemiballism, a form of violent involuntary proximal limb movement. For the same reason, lesioning is not performed at the STN as a form of ablative therapy. The risk of developing post-operative deficits is increased in elderly patients. Bilateral lesionings are also associated with significant morbidity and is generally not advocated. For patients with bilateral symptoms, unilateral procedures may sometimes benefit the ipsilateral side, albeit to a lesser extent than the contralateral side.

Pallidotomy

Pallidotomy is indicated if the patient has previously showed response to L-dopa but has subsequently developed intractability.[8] The best target is the most posterior and ventral part of the GPi. Contrary to thalamotomy, pallidotomy improves mainly bradykinesia and rigidity with shortening of the 'off' periods (92% of patients). Levo-dopa induced dyskinesia is also reduced. Tremor, on the other hand, is relatively less affected (81%).[3] Overall improvement in motor and activities of daily living can be achieved in 70 to 84% of patients.[9] Specific complications include injury to the internal capsule causing contralateral weakness. Injury to the optic tract, which lies ventral to GPi, may result in central visual field defect.

Chronic deep brain stimulation

Principles and techniques

It has long been realized that high frequency stimulation (> 100 Hz) at Vim can arrest tremor and that stimulation can give rise to similar behavioural effects as lesioning. Although its physiological basis is still unknown, chronic deep brain stimulation has developed as an alternative to ablative therapy over the recent years. It uses the same target localization principle as for lesioning. But instead of causing a lesion, a stimulation probe is left permanently in-situ after target localization and an electrical lead is brought out and connected to an external stimulator. A period of post-operative test stimulation is carried out in order to assess the clinical effects and determine the optimal stimulation parameters. If clinical improvements can be obtained without unwanted side-effects, the electrical lead is then internalized and connected to a permanent and programmable stimulation generator implanted subcutaneously over the infraclavicular area. This internal generator is powered by a battery which has to be changed every 3 to 4 years. Based on clinical assessment, the stimulation parameters can be further adjusted using an external magnetic device.[10]

The advantage of chronic deep brain stimulation is that any unwanted side-effects can be readily reversed by adjusting or simply switching off the stimulation. The parameters can be changed according to disease progression and the technique does not exclude the patients from receiving other therapeutic intervention (e.g. transplantation). In contrast, the effect of ablative therapy is "one-off" and irreversible. The main disadvantages of chronic stimulation include the risks of infection and migration of the implant. There is also considerable added cost for the device and demand for long-term technical support and patient compliance.

Thalamic stimulation

Similar to thalamotomy, chronic thalamic stimulation at the Vim improves mainly contralateral tremor (83%) whereas other PD symptoms are less affected. There is minimal permanent morbidity although around one third of the patients may experience some transient neurological deficits.[11-12] In patients who have already received thalamotomy on one side but who also require treatment on the contralateral side, chronic thalamic stimulation can be considered as a safer alternative to lesioning, especially in the elderly.

Pallidal stimulation

Experience with chronic stimulation at the globus pallidus is still limited.[13-15] Initial results have

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demonstrated up to 70% improvement in motor functions. Unlike pallidotomy, both contralateral akinetic symptoms as well as tremor can be improved. The patients are often able to reduce their levodopa dosage which may at least partially account for the reduction in dyskinesia. Again, bilateral procedure are associated with lower morbidity with chronic stimulation than with lesioning.

Subthalamic nucleus stimulation

Experimental animal studies have shown that lesioning at the subthalamic nucleus (STN) can relieve parkinsonian symptoms.[16] Theoretically, the STN is more attractive than other aforementioned targets in terms of neuronal circuitry because of its multiple connections within and beyond the basal ganglion. Intervention at this site may therefore exert a more wide-spread effect. Indeed, chronic stimulation of the STN has been found to produce significant improvement in most PD symptoms including gait, speech and posture.[15,17] These last three symptoms are often refractory to ablative or stimulatory treatment at other targets. The procedure is relatively free of side-effects, except hemiballism, which is usually reversible by changing the stimulation parameters while still maintaining a certain degree of clinical benefit.

Stereotactic radiosurgery

Stereotactic radiosurgery using gamma-knife, is an alternative method of achieving selective deep brain ablation. The technique involves similar stereotactic principle as in the open technique. Lesioning is achieved by means of highly focused gamma irradiation. However, unlike in open surgery, radiosurgery does not allow electrophysiological localization. Accurate target localization is crucial for the success of PD surgery. Since target localization is much more dependent on electrophysiological rather than morphological means, there is much concern about the reliability of gamma-knife in the treatment of PD. Moreover, the lesion size is less predictable in radiosurgery than by radiofrequency lesioning and the clinical effects can not be assessed until the lesion 'matures' around 3 to 4 months after the procedure. Although early results had been disappointing,[18] a recent study which employed more refined techniques had demonstrated significant improvement in tremor and levodopa induced dyskinesia in around 86% of patients.[19] Morbidity was minimal and post-operative imaging studies of the lesions had shown a mean maximal deviation of only 1 mm from the intended targets. Nonetheless, the role of stereotactic radiosurgery in the treatment of PD remains highly controversial at present.

Transplantation

The methods described above so far aim at altering the physical manifestations of the disease without affecting its natural history. Cell transplantation, on the other hand, is an alternative approach to treat PD by replacing the dopaminergic neurones within the basal ganglion, and thereby reversing or compensating for the on-going neuro-degenerative process. Results of autologous adult adrenal medulla cell implants were initially encouraging.[20] Further controlled clinical trials, however, failed to demonstrate any systematic or lasting benefit. Graft function and survival was found to be poor and the technique has been largely abandoned.

Fetal neurones, on the other hand, are able to survive well, reinnervate and establish synaptic contacts with host neurones, and sustain many of the morphological and functional characteristics of normal nigral neurones following grafting into a patient with PD.[21] In fetal mesencephalic transplantation, the rostral mid-brain containing dopaminergic neurones is harvested from fetuses obtained from therapeutic abortions (6 to 8 weeks gestation). The graft is then injected into the desired brain location of the host stereotactically (e.g. caudate nucleus). Usually, nerve cells from 3 to 4 "donors" are required for each recipient. To date, more than 200 of patients with PD have been treated with this method and significant improvement in akinetic symptoms and motor function has been observed.[22-23] The exact mechanism at work is unknown but the clinical effects are often delayed in onset and progressive with time, signifying that actual reinnervation by the graft neurones may play an important role.[24] The technique is a promising new strategy for the treatment of PD despite the potential problems with infection and graft rejection. In addition, one cannot overlook the

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Key messages

1. Levodopa is the most efficacious form of symptomatic treatment but is associated with disabling side-effects and reduction in efficacy after prolonged administration.
2. Thalamotomy is most effective at relieving contralateral tremor whereas rigidity and bradykinesia respond best to treatment at the globus pallidus.
3. The subthalamic nucleus is a promising new treatment target.
4. Chronic stimulation has the advantage of being programmable but is more costly and labour-intensive than ablative therapy.
5. The role of gamma-knife is highly controversial.
6. Cell transplant may offer a cure in the future by actually altering the natural history of the disease.

associated ethical, legal and religious issues when implementing this treatment.

Conclusion

Surgery is a promising approach for the treatment of PD. It is currently an useful adjunct to medical therapy, and may even in the future stand as an alternative. Patient and treatment method selection based on symptomatology and surgical risk factors is of primary importance. Education for both patients and medical personnel dealing with the disease is crucial in bringing the techniques to their deserved level of acceptance and application. ■

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Public Education Committee News

In order to present a clear image to the public on "What is a Family Physician?" and "What is Family Medicine?", our College would like to hold a CONTEST on writing up the "DEFINITION of FAMILY MEDICINE" in BOTH **English** and **Chinese**.

For interested parties, please submit your entry before **31 March, 1999** to
Chairman, Public Education Committee
The Hong Kong College of Family Physicians
Room 701, 7/F., Hong Kong Academy of Medicine Jockey Club Building,
99 Wong Chuk Hang Road, Aberdeen, Hong Kong.
(Please mark [Contest on '*Definition of Family Medicine*'] on the envelope for our easy reference.)

Winner of the contest will be presented with a cash award of HK$2,000 which is generously donated by our President. The winning entry will be published in *The Hong Kong Practitioner*.