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SURGERY FOR MOVEMENT DISORDERS

Abstract: Movement disorders, such as Parkinson's disease, tremor, and dystonia, are among the most common neurological conditions these days that affect millions of patients. Although medications are the pillar of therapy for movement disorders, neurosurgery has played an important role in their management for the past 50 years. Surgery is now considered as a viable and safe option for patients with medically intractable Parkinson's disease, essential tremor, and dystonia. With this review was aimed to present the history, indication, technical aspects, outcomes, complications, and emerging neurosurgical approaches for the treatment of movement disorders

Key words: *Deep Brain Stimulation, Dystonia, Esential tremor, Globus Pallidus, Movement Disorders, Parkinson's disease, Subthalamic nucleus, Ventralis intermedius nucleus*

HISTORICAL PERCEPTIONS

Various surgical approaches, such as resection, lesioning, stimulation, and others, have been used to treat patients with movement disorders. It was Irving Cooper (1) that first reported the effects of ligation of the choroidal artery for Parkinson's disease (PD) in 1953. It was not until the introduction of stereotaxis by Spiegel et al. (2) in 1947, and later by Leksell (3) in 1949, that a more accurate, less invasive, and more consistent placement of lesions in various subcortical locations became really feasible. The development of stereotaxy led to a variety of lesioning procedures of the basal ganglia and the thalamus for the treatment of rigidity and tremor in the 1950s and 1960s. Various surgical techniques, lesion locations, lesion sizes, and outcomes were reported (4, 5). However, it was the advent of L-dopa in the mid–1960s and its significant clinical benefits that led to a dramatic decrease in surgery for PD. For the next 20 years, surgery for movement disorders was predominantly limited to thalamotomy (6–8, 9, 10) for the treatment of tremor and pallidotomy and thalamotomy for dystonia (11, 12). PD surgery was rarely performed during this time. It was not until the late 1980 s that there was a reemergence of interest in the neu-

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rosurgical treatment for PD due to the increasing realization of the limitations of PD medications and the side effects of L-dopa. This led to a resurgence of lesioning surgeries such as pallidotomies for PD. The initial Leksell (13) target of pallidal lesions for treatment of PD was modified and repopularized by Laitinen et al. (14). The ability of electrical impulses to modify functional outcome in certain brain regions was identified almost 200 years ago, in 1809, by Rolando (15).

Early explorations by Hassler et al. revealed that acute low-frequency stimulation during stereotactic exploration for ablation of the pallidum could augment tremor, whereas high-frequency stimulation at 25 to 100 Hz had the opposite effect (16). These observations paved the way for the future development of chronic electrical stimulation therapies for the management of movement disorders. The first systematic use of chronic deep brain stimulation (DBS) for the treatment of movement disorders is attributed to Bechtereva et al. (17) in Russia. Beginning in 1967, they reported benefits with chronic DBS of the thalamus, striatum, and pallidum. But it was not until the 1980 s that Brice and McLellan (18), Blond and Siegfried (19), Siegfried and Shulman (20), and Benabid et al. (21) published reports of the use of chronic electrical stimulation or DBS for the treatment of movement disorders, thus ushering in a new era of functional neurosurgery for movement disorders. DBS has similar efficacy as that reported with various lesioning procedures (e. g., pallidotomy, thalamotomy). However, the superior safety profile of DBS relative to lesioning procedures, particularly bilateral thalamotomy and pallidotomy, has made it the procedure of choice in countries where access to this technology is available DBS, with its inherent features of reversibility and adjustability, has gained popularity and emerged as the neurosurgical standard of care for movement disorders such as PD, dystonia, and essential tremor over the past 20 years

MECHANISM OF DBS

The placement of stereotactic lesions and DBS reflect two different methods of neuromodulation. Whereas lesioning destroys a given volume of tissue, DBS exerts a reversible electrical field on the surrounding nervous tissue elements. There appears to be a combination of inhibition of neurons, modulation of abnormal patterns of activity, and activation of axons Initial observations suggested that HF stimulation caused inhibition of the cellular activity in the nucleus, thereby mimicking a transient lesion-like effect. In summary, the growing literature demonstrates the complexity of the motor system and the potential mechanisms of DBS action. The prevailing hypotheses postulate inhibition at the neuronal level, activation at the axonal level, as well as interruption of excessive and abnormally patterned neuronal activity in the STN, GPi, and the interconnected components of the CSPTC network (22, 23).

CRITERIA FOR THE SELECTION OF SURGICAL PATIENT

In general, patients must be able to tolerate the various components of surgery and have the cognitive skills and social support structure to comply with the de-

mands of surgery and the postoperative care. Both the patient and the family members need to have a detailed understanding of reasonable outcomes, potential complications, and the multiple steps involved in the preoperative assessments, surgery, and perioperative and follow-up care. The patient and family should have realistic expectations about surgical outcome, and they should understand that the surgery will not cure the disease or stop its natural progression. Neurosurgery for movement disorders can provide improvements in disabling motor symptoms and motor function. Patients should be in stable overall health with respect to cardiac, pulmonary, and systemic conditions such as hypertension, diabetes, and cancer. Patients who require anticoagulants, such as warfarin or antiplatelet medication, must be able to tolerate complete withdrawal from these medications before surgery. Consultation with other medical specialists may be required before proceeding with surgery. Neuropsychological assessment is recommended as part of the preoperative assessment to determine candidacy for neurosurgical intervention for the treatment of movement disorders. The neuropsychological assessment should include assessment of cognition, neuropsychiatric symptoms, social support, and goals for surgery. Patients with severe cognitive dysfunction or dementia on neuropsychological examination should be excluded from surgical intervention. Patients with mild cognitive impairment or frontal dysexecutive syndrome may still undergo surgery, but these individuals should have a strong social support structure and receive extra counseling, along with family members, regarding the potential for increased risks for cognitive impairment and confusion postsurgery. Psychiatric conditions such as anxiety, depression, and mania must be identified and medically optimized by a specialist preoperatively. Neurosurgical intervention in patients with delusional psychosis or severe personality disorder, such as borderline personality disorder, is generally not recommended. Medically refractory patients with significant motor complications and disability can benefit from DBS of the STN or GPi. Neurosurgery has been shown to consistently benefit only patients with idiopathic PD. Atypical parkinsonism (supranuclear palsy, nigrostriatal degeneration, etc.) or other disorders with parkinsonian features have not been shown to respond favorably to surgery. In general, surgery is most likely to benefit symptoms affecting the extremities rather than axial symptoms that involve posture, balance, gait, and speech. Surgical candidates typically have more than one of the following symptoms: severe tremors; off-medication-related rigidity, freezing, dystonia, and bradykinesia; on-medication-related dyskinesias; and signifi-cantly disabling on-off-medication motor fluctuations. One of the most important predictors of neurosurgical treatment response is the patient's response to L-dopa. Patients who demonstrate a significant improvement in motor symptoms during L-dopa off-medication versus on-medication states are most likely to benefit from surgery. The only exception to this general rule involves tremor. Consequently, a formal off-on test of L-dopa responsiveness can be very helpful in the selection of the best surgical candidates.

Essential tremor is a benign condition (24, 25) that can be managed for many years with medications. In those patients who have disabling extremity tremor despite optimal medication management, surgery using the VIM target becomes an

option. In general, patients with resting and distal postural tremor fare the best with surgery, followed by those with proximal postural tremor. Patients with intention/action tremor tend to benefit to a lesser degree. The more proximal and the action/intention features of tremor are the most difficult and challenging tremor characteristics to treat surgically (26). Head, neck, and lower-extremity tremors are also more difficult to treat than upper-extremity tremors. Tremors involving the head, neck, and axial regions usually require bilateral surgery.

DBS offers a therapeutically viable option for patients with severe, primary dystonia and also for a small subset of patients with secondary dystonia. The key to favorable responses after DBS in patients with dystonia is proper patient selection. Patients who are refractory to all conservative measures, including medication trials (anticholinergics, baclofen, benzodiazepines, or other muscle relaxants) and botulinum toxin injections are potential candidates. Primary, generalized dystonia of DYT–1-positive (27) or non-DYT–1 types, as well as patients with idiopathiccervical dystonia can obtain the best motor benefits with bilateral GPi DBS (23). Patients with juvenile-onset idiopathic dystonia whose age of onset is older than 5 years and who do not have multiple orthopedic deformities also have a good response to surgery (29). Appendicular symptoms (e. g., those affecting the limbs) appear to respond better than axial symptoms (30). With regard to focal dystonia, ideal surgical candidates are those with cervical dystonia (30). The results of DBS for secondary dystonia are inconsistent. In general, DBS for secondary dystonia is less effective than for primary generalized dystonia, particularly in those patients with an identifiable structural brain abnormality. The only exception is tardive dystonia, which has been reported to respond well to surgery in a small number of patients (33).

SURGICAL TARGETS

The three most common targets for movement disorder surgery are the STN (subthalamic nucleus), GPi (Globus Pallidus interna), and VIM (Ventralis intermedius) thalamus. GPi and STN DBS improve PD symptoms (e. g., tremor, rigidity, and bradykinesia) and also reduce drug-induced dyskinesias. STN DBS also reduces the medication burden, thereby reducing medicationassociated side effects (31). Both the STN and the GPi have corresponding associative (cognitive), limbic, and motor territories that require accurate surgical targeting of the motor component. Presently, the most commonly used target for DBS therapy to treat PD is the STN, followed by the GPi. The GPi is also the most commonly used target for dystonia (32, 33). The VIM target is the main target used for non-parkinsonian tremor. The VIM is very effective in alleviating PD-associated tremors, but is not effective in the treatment of other cardinal PD symptoms. Thus, VIM DBS surgery is rarely performed for PD treatment.

The STN was previously not considered a target because of the fear of causing hemiballismus. However, in 1990, Bergman et al. (34) showed that a lesion in the STN of a nonhuman primate model could reverse the symptoms of PD. This early work, coupled with the evolving concept of the flexibility (e. g., reversibility and

adjustability) inherent in DBS for the treatment of movement disorders, resulted in Benabid et al. (35) and Pollak et al. (36) applying STN DBS for the treatment of PD initially in 1993, with report of a subsequent case series in 1995 (37). Anatomically, the STN (also called the corpus luysi) is an almond-shaped nucleus located on the inner surface of the peduncular portion of the internal capsule. The STN is surrounded by several key structures that need to be considered carefully. This includes the anterior and laterally situated internal capsule, through which corticospinal and corticobulbar fibers pass. Anteromedially lie the fibers of Cranial Nerve III, the posteromedial hypothalamus, and portions of the fields of Forel. The red nucleus, fibers with cerebellothalamic projections, and the prelemniscal radiations are situated posteromedially. Dorsal to the STN is the zona incerta and Forel's field H2 that separate it from the ventral border of the motor thalamus. The cerebral peduncle and the substantianigra are situated ventral to the STN.

The GPi target is used for PD treatment less commonly than the STN. However, the GPi is currently the most common target for treating dystonia (38) despite reports of using thalamic (Voa, ventrolateral) (39) and subthalamic DBS targets (40) for dystonia. The GPi DBS target is the posteroventrolateral GPi, which is the predominant motor territory of the nucleus. The therapeutic sensorimotor territory of the GPi is ventral and posterior, and the somatotopy places the face and arm posterior and ventral, and the leg central and more dorsal (41)

The VIM is the common lesioning and DBS target used for the treatment of tremor (42, 43). In the somatotopic organization of the VIM nucleus face, responsive cells lie medially, followed by the upper extremity more lateral, and the lower extremity is the most lateral, situated closely to the internal capsule. The VIM nucleus of the thalamus has neurons that fire in synchronous bursts with the tremor frequency and are called tremor cells (TCs). The DBS target for tremor control is the electrophysiologically defined VIM (44). This electrophysiologically defined motor thalamus (VIM) has TCs and kinesthetic cells, and it lies immediately anterior to the cutaneous receptive cells, which lie in the sensory thalamus (44). The somatosensory relay nucleus ventralis caudalis (VC) of the thalamus lies immediately posterior to VIM. The VC has specific neurons that respond to tactile stimulation in small, receptive fields.

OUTCOMES OF DBS FOR MOVEMENT DISORDERS

Prospective studies have reported on the outcomes of GPi and STN DBS for the cardinal symptoms of PD. Both targets are shown to be beneficial (45), although a trend exists among these studies to indicate that STN DBS is more effective. In addition, STN DBS tends to allow for a greater reduction in the postoperative medication burden with consequent reduction in dyskinesias (46). Direct comparisons of GPi versus STN stimulation have been performedin small samples of patients. The outcome data from these studies were not conclusive enough to exclude the GPi as an accepted DBS target for PD (31) and generally corroborated the advantage of using the STN in improving UPDRS Part III scores and L-dopa intake (47). In ad-

dition, a recent report of long-term bilateral pallidal stimulation in 11 PD patients confirmed the therapy's sustained efficacy in alleviating dyskinesias. However, motor scores that had been alleviated in the first year deteriorated during the 5-year follow-up to an extent greater than would be expected from disease progression alone. The lost motor benefits were not regained with additional programming, but were successfully recaptured in four patients by repositioning the electrodes from the GPi to the STN (43). It is possible that STN stimulation is more prone to cognitive and behavioral complications. The encouraging results of STN DBS originally reported by Benabid and the pioneering Grenoble group (49–51, 52) motivated a large number of studies in the past decade that have further validated the safety and efficacy of this procedure (53, 54).

Stereotactic thalamotomies targeted at the VIM nucleus are well-established procedures for the management of tremors from PD or essential tremor (10). In managing patients with PD, thalamotomies alleviate tremors without significantly affecting the other cardinal symptoms of PD. Unilateral thalamotomies are considered relatively safe, but bilateral procedures carry an elevated risk of neurological deficits such as dysarthria and cognitive deterioration (55). Chronic stimulation was considered a potential alternative to thalamotomy, at least partly because the known tremor-alleviating effects of acute stimulation were used for physiological confirmation during ablative stereotactic interventions (56). In addition, thalamic chronic stimulation had already been demonstrated to be feasible and safe for patients undergoing stereotactic interventions for chronic pain conditions (57–59). DBS, initially considered an alternative to stereotactic thalamotomy, gradually became the surgical procedure of choice for the treatment of essential tremor, as it demonstrated similar efficacy rates and lower risks (10). A direct comparison between thalamotomy and thalamic stimulation was reported by Schuurman et al. (60). The vast majority of thalamic DBS procedures have been targeted at the upper extremity function. However, lower extremity, head/neck, and axial tremor are also common problems that negatively impact quality of life for patients with essential tremor. Putzke et al. (61) reported on the outcomes of 22 patients with head, voice, or trunk tremor undergoing bilateral, staged, DBS thalamic implants. Bilateral stimulation was more effective than unilateral stimulation in alleviating axial tremors; however, as for bilateral thalamotomies, the rate of neurological complications was higher in patients who underwent bilateral stimulation. Dysarthria was observed in 27% of patients with bilateral stimulation, whereas none of those undergoing unilateral stimulation experienced the same problem. Likewise, disequilibrium was more common during bilateral stimulation.

Stereotactic ablative surgery of the GPi (pallidotomy) has been attempted in the past in patients with generalized dystonia. Encouraging results have been reported (11) but, unlike reports of thalamotomies for treating tremor, the best results are not observed immediately, but rather, after several weeks or months (62). Unilateral and, in particular, bilateral pallidotomies may carry a higher risk of neurological morbidity, including lethargy and hemiparesis (63), even in the absence of hemorrhagic complications.

In summary, GPi or STN DBS has been demonstrated to be effective in alleviating the symptoms of medically refractory PD in multiple reports in the literature. These results were confirmed by prospective series with double-blinded assessments and were largely sustained at 5-year follow-up evaluations. A trend exists in favor of STN versus GPi DBS that must be verified once the outcome of additional studies comparing GPi and STN is available.

Chronic stimulation of the VIM thalamus has become the procedure of choice for the treatment of tremors because of its associated high efficacy rates and low risks. VIM DBS is also highly effective for PD tremor, but it is rarely performed today for PD because both STN and GPi DBS significantly improve tremor as well as other manifestations of PD. Patients with axial tremors tend to benefit from bilateral stimulation, which carries a higher risk of adverse neurological effects. Bilateral pallidal (GPi) DBS is safe and effective for alleviating primary generalized and segmental dystonia, but the results may not be evident until after several weeks or months of stimulation. Patients who are positive for the DYT–1 mutation and those with disease of early onset may experience greater benefits.

COGNITIVE AND NEUROBEHAVIORAL OUTCOME AND COMPLICATIONS WITH DBS

The vast majority of data documenting neurobehavioral outcomes after DBS involve patients who underwent surgery in the STN. The most common neuropsychiatric side effect in the immediate postoperative period after STN DBS is transient confusion, with an incidence that ranges between 1 and 36% (64). Evidence of greater neuropsychological deficits before surgery is significantly associated with increased confusion after surgery (65). Neuropsychiatric symptoms have also been reported after STN DBS, and several studies have reported hypomania, depression, apathy, and suicidality (66). Postoperative hypomania was reported in 4 to 15% of STN patients in four studies (67), and postoperative depression has been reported to occur in up to 1.5 to 25% of patients (68). The extent to which medication changes after surgery contributed to the reported changes in mood state is not well known. The neurobehavioral outcome literature after DBS in the GPi and VIM is much more limited than that pertaining to STN DBS. Many studies examining cognitive and neuropsychiatric outcomes after GPi DBS documented no significant declines. Isolated studies identified mild declines on measures of word fluency and visuoconstructional skills (66). There are very few studies examining neurobehavioral outcomes after VIM stimulation, and interpretation of the available data is confounded by small samples of patients with mixed diagnoses. In general, most of the data revealed no significant cognitive or neuropsychiatric declines.

COMPLICATIONS OF DBS SURGERY

Understanding the complications of any surgical procedure helps in anticipating, preventing, recognizing, and promptly intervening on such occasions. The

complications of DBS surgery can be mainly classified into four categories. These include intracranial hemorrhages, infections, hardware-related issues, and stimulation-related complications.

Intracranial hemorrhage is one of the most important complications of movement-disorder surgery. Intraoperative hemorrhages are reported to occur in 0.2 to 12.5% of all STN DBS cases (69). Hemorrhages can be extradural, subdural, and intraparenchymal. Intraparenchymal hemorrhages are the most common and typically occur in the tract of the electrode or in the periventricular region in close proximity to vessels associated with the ventricles. The size of the hemorrhages is generally small. There is little agreement on the predictors of intraoperative hemorrhages in patients who undergo DBS. The common factors identified include: 1) High blood pressure: the practices of carefully controlling blood pressure and painstakingly planning the trajectory, avoiding vasculature seen on the contrast-enhanced preoperative images, help reduce the incidence of hemorrhages. There is a statistically significant association of hemorrhagic complications with hypertension (70). Bleeding occurs in 10.71% of hypertensive patients and 0.91% of those who were normotensive (P 0.0111). The same study also documents that the combination of MER and hypertension increases the risk of hemorrhage to 16.67% (70). 2) MER: an increased incidence of bleeding in hypertensive patients who underwent MER (P 0.034) was observed by Gorgulho et al. (70). There are reports that strongly implicate MER as a risk factor for hemorrhage (71), and there are studies that state otherwise (72). It is difficult to draw any conclusion from the available literature pertaining to increased risk of hemorrhage with MER. 3) Target: some studies have documented that the GPi is more prone to hemorrhagic complication compared with the STN or the thalamus. Binder et al. (73) have shown a 7% risk of GPi hemorrhage compared with 2.2% risk of STN hemorrhage. In 2001, the DBS study group reported similar results (GPi, 9.8%; STN, 2.9%) (70). It has been suggested that anatomic peculiarity of the vasculature in the GPi region may be responsible for the increased incidence of hemorrhage (73). The GPi is supplied by the lenticulostriate arteries that come from the anterior circulation. These arteries are more prone to the effects of hypertension and may also be developmentally different (73). 4) Trajectory planning: the use of image fusion of CT and MRIscans helps in performing accurate targeting. The images that help most in avoiding hemorrhagic complications are the postcontrast T 1-weighted MRI scans. These images reveal small paraventricular, sulcal, intraventricular, and ependymal vessels and assist with the planning of a vessel-free trajectory.

Reported infection rates for DBS surgery vary widely, from less than 1% to as high as 15% (74, 75). This is probably because different clinical definitions are used for identifying infection. The criteria for diagnosing infections are not well defined in the reported literature. DBSrelated infections have a variable presentation in terms of time and location. Typically, the infection presents within 3 months after surgery, and the most common site was at the IPG) (75). Infections of the IPG tend to present soon after surgery, as do infections at the burr hole. Infections at the connector may be related to erosions. This scenario was more common in the past,

when the extension connectors were larger. The introduction of the lower-profile extension connector has significantly reduced the incidence of erosions. Clinically, the infections presented as cellulitis, erythema, drainage, dehiscence, or stitch abscess. The common bacterial pathogens isolated are Staphylococcus aureus, S. epidermidis, Serratia sp., Klebsiella sp., and sometimes, Escherichia coli and mixed flora. Most of the published data fail to address any specific predictors for the infections. The risk of brain abscess from DBS infection is extremely low, with only one case reported (76). The important management decision is whether to remove or keep the hardware.

Hardware-related complications are the most common, with a varying incidence that ranges from 2.7 to 50%, (77). These include DBS electrode fracture, extension wire failure, lead migration, skin erosion, IPG malfunction, and pain over the pulse generator (69). They can be subdivided into complications associated with the lead, those associated with the extension wires, and the IPG (75). Because the brain lead is the most delicate part of the hardware, it can malfunction or get damaged due to a variety of causes. These include lead fracture, lead erosion, and lead malfunction. The fractures are most often the result of a fall or trauma. However, fractures can occur secondary to migration of the connector to the neck (78) or even with unusual conditions, such as compulsive twisting (79). Lead erosion is not commonly observed and is usually caused by superficial placement of the lead. Lead malfunctions are generally related to connector migration in the cervical region that causes stress on the lead and results in multiple open or short circuits. Complications associated with extension wires are more uncommon than of the DBS lead because the extension material is more robust. Extension wire complications include erosions (if placed superficially), fractures, and pain and/or tightness that result from superficial placement (75). Complications associated with the IPG include erosion, caudal migration of IPGs, and shocking sensations at the IPG site (75). Subfascial implantation of the IPG is an alternative to subcutaneous implantation and may be advantageous in very thin patients. The most common stimulation-induced complications are dyskinesias, worsening of axial symptoms, speech dysfunction, capsular stimulation, and ocular symptoms.

DBS is currently the best surgical approach for movement disorders with respect to safety, efficacy, and proven track record. However, DBS is an implantable device, with its associated complications, and it treats the symptoms of the patient and not the underlying disease. In this context, restorative strategies aimed at treating the underlying disease pathophysiology are important.

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