Deep brain stimulation in the treatment of dyskinesia and dystonia

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Deep brain stimulation (DBS) has become a mainstay of treatment for patients with movement disorders. This modality is directed at modulating pathological activity within basal ganglia output structures by stimulating some of their nuclei, such as the subthalamic nucleus (STN) and the globus pallidus internus (GPi), without making permanent lesions. With the accumulation of experience, indications for the use of DBS have become clearer and the effectiveness and limitations of this form of therapy in different clinical conditions have been better appreciated. In this review the authors discuss the efficacy of DBS in the treatment of dystonia and levodopa-induced dyskinesias. The use of DBS of the STN and GPi is very effective for the treatment of movement disorders induced by levodopa. The relative benefits of using the GPi as opposed to the STN as a target are still being investigated. Bilateral GPi stimulation is gaining importance in the therapeutic armamentarium for the treatment of dystonia. The DYT1 forms of generalized dystonia and cervical dystonias respond to DBS better than secondary dystonia does. Discrimination between the diverse forms of dystonia and a better understanding of the pathophysiological features of this condition will serve as a platform for improved outcomes.

KEY WORDS • dystonia • dyskinesia • Parkinson disease • deep brain stimulation • stereotactic neurosurgery

Long-term electrical stimulation is being used increasingly in patients with movement disorders whose disability continues despite medical treatment. Because of its effectiveness and potential reversibility, in many regions of the world DBS has gradually replaced lesioning procedures for the treatment of PD, dystonia, and essential tremor. With the accumulation of experience, the indications for DBS have become clearer and the effectiveness and limitations of this form of therapy are being better appreciated. Although DBS has multiple applications, we will limit this discussion to DBS for dyskinesias induced by levodopa therapy and for dystonia.

USE OF DBS FOR LEVODOPA-INDUCED DYSKINESIAS

Dyskinesias induced by long-term levodopa therapy represent one of the major limitations in the treatment of patients with PD. These involuntary choreiform and dystonic drug-induced movements constitute a common problem for which the incidence is as high as 80% after 5 years of treatment.⁵⁸ Most patients with PD who have dyskinesias become significantly disabled by these abnormal

movements that are caused by long-term medication treatment and disease progression. Both lesioning and high-frequency stimulation in the GPi and STN can be effective in the treatment of these abnormal movements.

Stimulation of the STN. The improvement in dyskinesias after DBS of the STN is probably related to two mechanisms: the first is the reduction in medication that often occurs after surgery and the second is a direct anti-dyskinetic effect. The mean levodopa-equivalent dose intake used preoperatively is reduced by 50 to 60% after DBS of STN.^{5,24,29,30,33,48,52,56,62,66,77,80} Along with this reduction in medications, Unified PD Rating Scale Part IV (complications of therapy) scores improve by 70 to 95% after 6 months in patients treated with STN stimulation.^{5,66,80} The duration of dyskinesias is reduced by 70 to 85% after DBS of the STN and there are significant improvements in both disability (by 58–93%), and motor fluctuations (by 45–61%).^{5,16,24,29,30,33,48,52,56,62,66,70,75} The improvement in dyskinesias is sustained at 5 years after surgery of the STN for DBS.³⁰

Stimulation of the GPi. Stimulation of the GPi has a strong, direct effect on reducing or eliminating levodopa-induced dyskinesias that is independent of any reduction in medications after surgery.^{16–18,31,79} There is a 65 to 75% reduction in dyskinesia scores, and the duration of these symptoms throughout the day improves by 65 to 70% at 3 to 6 months after pallidal DBS.^{16,17,31,79} The 50% reduction in dyskinesia scores remained at 3 years after pallidal DBS.¹⁸

Abbreviations used in this paper: DBS = deep brain stimulation; GP = globus pallidus; GPe = GP externus; GPi = GP internus; PD = Parkinson disease; STN = subthalamic nucleus.

The relationship between the location of the stimulating electrode's contacts in the GP and the clinical effect of DBS is somewhat complex and controversial. The best location within the GP for the treatment of dyskinesias seems to be the ventral portion of the GPi. Some groups have reported that stimulation of the GPe and the dorsal border of the GPi improves akinesia and worsens dyskinesias.^{6,17,31} The results of GPi stimulation can be optimized by adjusting the device's parameters and carefully choosing among the multiple contacts on the DBS electrode within the GPi.

Targets for the treatment of dyskinesias and PD. The issue of whether the GPi or the STN is a better target for the treatment of advanced PD and levodopa-induced dyskinesias is still debated.^{16,32,36,40,77} The GP is a larger structure and there is more heterogeneity in its response to surgical interventions.⁴ This is probably related to variations in the position of the stimulating electrode contacts in the pallidal complex.^{22,45} In contrast, the STN is smaller and appears to provide more consistent results.⁴⁶ In the only prospective randomized study published so far, Burchiel, et al.,¹⁰ have shown that after 1 year dyskinesias were improved by 67% with DBS of the STN and by 47% with DBS of the GPi. This difference was not statistically significant because the study was underpowered; it included only 10 patients. A multicenter prospective non-randomized cross-over study showed that dyskinesia scores improved by 58% with DBS of the STN and by 66% with DBS of the GPi at 6 months.¹⁶ The time spent in the "on" condition with dyskinesias was reduced by 69% with DBS of the STN and by 65% with DBS of the GPi at 6 months. Randomized double-blinded trials will be necessary to evaluate the relative effectiveness of each of these approaches in the treatment of levodopa-induced abnormal movements.

USE OF DBS FOR DYSTONIA

Dystonia Types. Dystonia is a syndrome of sustained muscle contractions that produces twisting and repetitive movements and abnormal postures.²⁰ Various forms of dystonia have been described, most of which are refractory to medical therapies. In this context, DBS has been used to treat several of these conditions but its efficacy varies according to the type of dystonia.

The common form of inherited generalized primary dystonia is the DYT1 form (Oppenheim dystonia). It is caused by a single GAG deletion in the *DYT1* gene,⁵⁴ which is localized on chromosome 9q34⁵³ and encodes torsin A, a member of the family of AAA adenosine triphosphatases. The inheritance pattern of the *DYT1* gene mutation is autosomal dominant but the phenotypic penetrance is 30 to 40%.⁹ The *DYT1* mutation is more common in Ashkenazi Jewish populations but has also been found in non-Jewish North American, European, and Asian families.^{9,49} Patients with DYT1 dystonia usually present in childhood with limb dystonia that may subsequently generalize. Craniocervical involvement is unusual in this disorder.⁵³

Cervical dystonia is a common form of primary dystonia. It presents with sustained contractions of the cervical

musculature that lead to twisting and abnormal postures of the neck.³⁶ Dopamine D₅ receptor dysfunction has been implicated in this disorder.^{8,57} Compared with DYT1 and idiopathic cervical dystonia, the responses of non-DYT1 primary dystonias and secondary dystonias to surgery are variable.^{1,7,13,15,19,27,34,36,37,47,59,71,83} Nonetheless, several patients with a variety of non-DYT1 dystonias and secondary dystonias, such as those seen in Hallervorden-Spatz syndrome,^{73,80} have benefited from GPi lesioning or DBS.^{28,35,44,64,69,74,81}

Use of Stereotactic Surgery for Dystonia. The surgical treatment of dystonia has a long history, beginning in the 1950s. In the past, the most common target for ablation was the thalamus. In one of the largest series of patients with dystonia who were treated with thalamotomies, Cooper¹⁴ reported an overall improvement in 70% of cases. Nevertheless, his procedures varied in location within targets, by number of lesions, number of repeated procedures, methods of ablation, and targeted nuclei, including the nuclei ventralis oralis anterior, ventralis oralis posterior, and ventralis intermedialis, and centromedian, the pulvinar, and portions of the nucleus ventralis posterolateralis. Studies in which patients with dystonia were further subdivided according to type have shown that thalamotomies improved the dystonic symptoms in 25 to 80% of patients with generalized dystonia, in 33 to 62% of those with focal/segmental dystonia, in 35 to 60% of patients with primary dystonia, and in 34 to 63% of those with secondary dystonia.^{2,11,21,63,65,84} The nuclei ventralis intermedialis,^{2,65} ventralis oralis posterior,⁶⁵ and the transitional nucleus ventralis oralis anterior/posterior,^{11,84} were the most common targets chosen for ablation. The major limitation of thalamotomies, particularly when they were performed bilaterally, was the high incidence of complications including speech problems, motor weakness, and pseudobulbar palsy.^{2,11,21,63,65,84} Even though in some of the older studies the GPi has also been reported as a target,^{14,23} pallidal procedures for the treatment of dystonias have only recently regained attention.^{26,47}

Stimulation of the GPi. Patients with dystonia who have significant disability and whose condition is resistant to pharmacotherapy are considered to be surgical candidates. The main advantages of pallidal stimulation over pallidotomy are reversibility and the ability to adjust the desired parameters of stimulation. These characteristics may be important in younger patients or patients with secondary dystonia in whom structural lesions already exist in the basal ganglia. Surgery is usually performed after induction of local anesthesia, but for children and patients with severe postural abnormalities it may also be performed after general anesthesia is induced or intravenous sedation administered.

Physiological localization with microelectrode recordings is important to identify the following structures: 1) the sensorimotor territory of the GPi, in which neurons respond to active and passive movements of the body and limbs; 2) the optic tract that lies ventral to the GPi; and 3) internal capsule fibers that are apposed to the medial and posterior border of the GPi. The properties of pallidal neurons in patients with dystonia are still controversial.^{25,76} Vitek, et al.,⁷⁶ found that neurons in both the GPe and the GPi in patients with dystonia fired at lower frequencies

compared with the firing rate in patients with PD. In that study, somatosensory responses in the GPi of patients with dystonia were similar to those reported for PD; the neurons fired in conjunction with movement in multiple directions and in multiple joints. Hutchison, et al.,²⁵ reported that the firing rates of pallidal neurons in patients with dystonia were similar to those described in PD but that there were some differences between these disorders in the firing pattern and neuronal bursting. Sanghera, et al.,⁶⁰ reported that the GPe and GPi neurons displayed similar discharge rates and patterns in patients with dystonia, whereas in patients with PD, the discharge rate of GPe neurons was lower than that in GPi neurons. Lenz, et al.,⁴¹ suggested that GPi neuronal activity was inversely correlated with the severity of dystonia in a patient undergoing pallidotomy. Additional studies will be necessary to arrive at a better understanding of the pathophysiology of dystonia.

Outcome of DBS. Primary generalized DYT1 and idiopathic cervical dystonias appeared to be more responsive to DBS.^{1,7,13,15,19,27, 34,36,37,47,59,71,83} Furthermore, patients with primary generalized dystonia have a more pronounced response to DBS of the GPi than do patients with secondary dystonia.^{13,15,19, 44,61,67,73} The improvements in patients with DYT1 dystonia after pallidal stimulation are remarkable: the reductions of symptoms ranged from 20 to 90% on the Burke-Fahn-Marsden Dystonia Rating Scale at 6 to 12 months.^{13,15, 19,47,59,71} Although unilateral procedures are effective for contralateral limb dystonia, bilateral electrodes are required to improve axial dystonic symptoms.^{51,76,84} The percentage of improvement in the Burke-Fahn-Marsden Dystonia Rating Scale score has been reported to be between 46 and 79% in primary dystonia at 3 to 12 months of follow up^{19,26,47,51,76} and much lower, between 4 and 34%, in secondary dystonia at 6 to 16 months follow up.^{19,42,43,51} Patients with cervical dystonia treated with pallidal DBS improve by 40 to 80% according to the Toronto Western Spasmodic Torticollis Rating Scale.^{1,7,12,19,27,34,36,55,83} Pain is usually the first symptom to respond followed by improvements in motor disabilities and severity of symptoms. Predicting the outcome in patients with primary generalized non-DYT1 dystonia or secondary dystonia is much more difficult.^{13,15,19,44,61,67,73}

The deep brain stimulators for dystonia may require longer pulse widths (> 210 μ sec) compared with those used for PD (60–90 μ sec).^{38,82} Even though it has been stated that the initial improvement in the acute phase of the postoperative period is an indicator of long-term prognosis after pallidal surgery,^{15,38,67,73,78} in our experience the benefits experienced by the patients with dystonia gradually build up in a delayed and progressive manner over time.¹⁹ Thalamic DBS is also said to improve dystonia,^{3,50,61,72} but the benefits obtained with stimulation in that location seem to be less prominent than the ones achieved with pallidal stimulation.^{39,68}

CONCLUSIONS

Deep brain stimulation of the STN and GPi is very effective for the treatment of movement disorders induced by levodopa. The relative benefits of using the GPi or

STN as targets are still under investigation. Bilateral GPi stimulation is becoming important in the therapeutic armamentarium for the treatment of dystonia. Some forms of dystonia respond better than others, particularly the *DYT1* mutation forms of generalized dystonia and cervical dystonia. In the future, discrimination between the diverse forms of dystonia and a better understanding of the pathophysiological features of this condition will serve as a platform for improved outcomes of therapy.

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