

# Long-term high-frequency bilateral pallidal stimulation for neuroleptic-induced tardive dystonia

## Report of two cases

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✓ The authors report the results of long-term bilateral high-frequency pallidal stimulation in two patients affected by neuroleptic-induced dystonia.

The first patient, a 33-year-old man, experienced a dystonic posture of the trunk, with involvement of the neck and upper and lower limbs after 11 years of treatment with neuroleptic drugs. The second patient, a 30-year-old man, presented with a torsion dystonia, spasmodic torticollis, and involuntary movements of the upper limbs, which appeared after 4 years of neuroleptic treatment. Both of these dystonias worsened even after the neuroleptic treatment had been discontinued, and neither patient responded to clozapine or benzodiazepine therapy. The time lapse between the first appearance of dystonia and surgery was, respectively, 5 and 3 years. In each case bilateral stereotactic implantation of electrodes within the globus pallidus internus (GPI) was performed while the patient was in a state of general anesthesia. The electrodes were placed at the following anterior commissure–posterior commissure line–related coordinates: 20 mm lateral to the midline, 6 mm below the intercommissural plane, and 3 mm anterior to the midcommissural point. Electrical stimulation (130 Hz, 1 V, 90  $\mu$ sec) was begun on the 1st postoperative day. In both patients, a genetic analysis positively ruled out a mutation in the *DYT1* gene, and magnetic resonance imaging yielded normal findings in both cases.

Extrapyramidal symptoms and dystonia disappeared almost completely and dramatically in both patients just a few days after high-frequency bilateral pallidal stimulation commenced. Both patients regained autonomy and neuroleptic treatment was reinitiated. The follow-up period for both cases was 1 year. Long-term bilateral high-frequency stimulation of GPI resulted in a dramatic and long-lasting improvement of neuroleptic-induced tardive dystonia.

**KEY WORDS** • tardive dystonia • deep brain stimulation • globus pallidus internus • neuroleptic drug

THE term “dystonia” refers to a clinical syndrome characterized by sustained muscle contractions that frequently cause twisting, repetitive movements, or abnormal postures. Dystonia can be caused by acquired lesions (secondary dystonia) or neurodegenerative processes of the central nervous system (heredodegenerative dystonia), or it can occur in the absence of any identifiable cause (primary dystonia).<sup>11,26</sup> Tardive dystonia was first recognized and described in 1982 by Burke, et al.,<sup>3</sup> as a specific clinical syndrome distinguishable from tardive dyskinesia. These authors provided five diagnostic criteria. 1) Chronic dystonia must be present. 2) If other involuntary movements are present, dystonia is the primary affecting syndrome. 3) Dystonia develops during or within 2 months of neuroleptic drug withdrawal. 4) Other causes of secondary dystonia have been adequately ruled out. 5) There

is no family history of dystonia.<sup>3</sup> Because nearly 1% of the world’s population is known to suffer from schizophrenia and neuroleptics are widely used to treat this disorder, the incidence of side effects in this population may be expected to be substantial. It has been reported that the incidence of irreversible tardive dystonia following neuroleptic therapy can be as high as 1 to 4%.<sup>37</sup> Although exposure to neuroleptics is known to be the most significant prognostic factor,<sup>9,10,39</sup> other drugs, such as prochlorperazine, promethazine, metoclopramide, amoxapine, and veralipride, have also been reported to cause this type of dystonia.<sup>8,14,18,19</sup> The exposure to an antipsychotic medication does not necessarily need to be long<sup>16</sup> and the presence of a minimum safe period of use does not appear to exist. Tardive dystonia has been described to develop even after a few days of treatment with neuroleptics.<sup>3</sup> To date, the pathophysiology of tardive dystonia has not been elucidated and the treatments that are presently available are notoriously disappointing. The first step in this treatment involves the gradual withdrawal of the provoking medications and substitution of newer, “alternative” neuroleptics such as clozapine. Despite neuroleptics withdrawal, however, there are some cases of tardive dystonia in which the symptoms appear to become

*Abbreviations used in this paper:* AC = anterior commissure; BFMDRS = Burke-Fahn-Marsden Dystonia Rating Scale; CT = computerized tomography; DBS = deep brain stimulation; FOV = field of view; GPI = globus pallidus internus; MR = magnetic resonance; PC = posterior commissure; VIM = ventralis intermedialis nucleus.



FIG. 1. *Upper:* Movie frames obtained from a preoperative video showing the patient in Case 2 walking. *Lower:* Movie frames obtained from a postoperative video showing the same patient 3 days after surgery.

irreversible and resistant to any pharmacological treatment, including benzodiazepines and botulinum toxin injections.

In this report we describe two cases of tardive dystonia in which long-term bilateral high-frequency pallidal stimulation was used as a therapeutic intervention. We report that there was a dramatic, long-lasting improvement in each of these cases.

## Case Report

### *Preoperative Case Summaries*

*Case 1.* This 33-year-old man, who was 16 years of age when schizophrenia was diagnosed, had no family history of neurological disease or movement disorders and had a completely normal pattern of motor and cognitive development.

The patient had been treated with neuroleptic drugs (haloperidol, pimozide, and risperidone) since the initial onset of his psychiatric symptoms. At the age of 28 years, he began to experience a slight trunk dystonia that became more pronounced when he was walking. His neurological condition began to deteriorate when he was 32 years old, at which time a more evident dystonic posture of the trunk, with involvement of the neck and upper and lower limbs, and a subsequent functional impairment began to develop. Treatment with anticholinergic drugs proved to be ineffective and the neuroleptic drugs were discontinued. No change in the patient's dystonia occurred, but there was a worsening of his psychiatric symptoms.

At the time of surgery, the patient's neurological examination revealed a generalized dystonia, which was characterized by a mild oral mandibular and trunk dystonia, torticollis, and dystonic postures of his upper limbs and his left lower limb, which were present during walking (BFMDRS<sup>4</sup> Score 36).

*Case 2.* This 30-year-old man was the second child of healthy parents. He had been healthy until the age of 21 years when he presented with severe phobic symptoms accompanied by frequent panic attacks that were quite disabling. His initial treatment consisted of benzodiazepine and antidepressant medications that had no effect. When he was 25 years old, neuroleptic therapy (haloperidol) was started with good results. After 2 years, however, an abnormal posture of his head began to develop, although this symptom was intermittent. His condition markedly worsened when

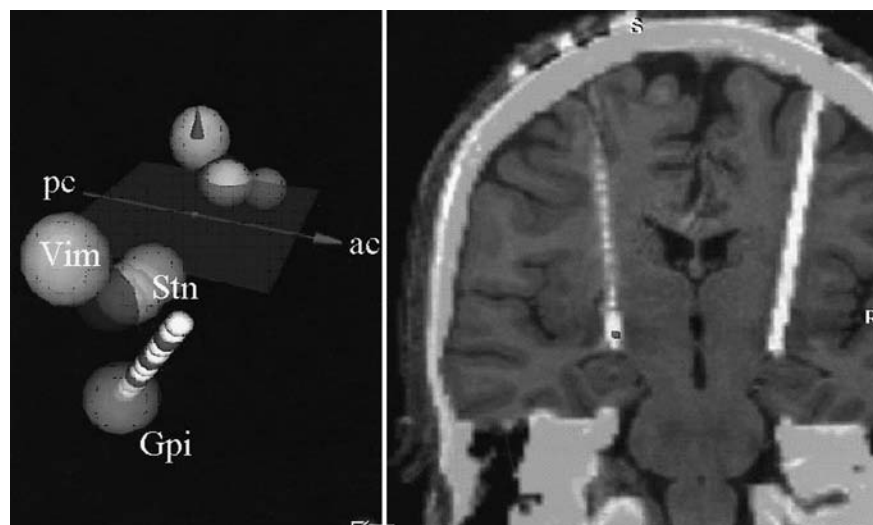


FIG. 2. *Left:* Three-dimensional computerized graphic model of the targeted nuclei registered to the AC-PC line and the intercommissural plane. The distal contact electrode is implanted within the Gpi nucleus. *Right:* Postoperative assessment of implanted electrodes by image fusion of a postoperative CT scan with the corresponding preoperative inversion-recovery image. Stn = subthalamic nucleus.

TABLE 1  
Clinical data and postoperative results in two patients with tardive dystonia

Case No.	Age (yrs), Sex	Suggested Causative Drug	Duration of Disease (yrs)	BFMDRS Preop Score	Clinical Presentation at Surgery	(%) Improvement
1	33, M	haloperidol, pimozide, & risperidone	5	36	generalized dystonia, torticollis, oral mandibular dystonia, trunk, upper limbs, & lt lower-limb dystonia during walking	42
2	30, M	haloperidol	3	70	generalized dystonia, fixed retrocollis & tortipelvis, dystonia of lower limbs, & dystonic spasms involving the axis	78

he reached 28 years of age, with the development of a severe retrocollis and involvement of the trunk and lower limbs (Fig. 1). The neuroleptic drugs were discontinued, but this had no effect on the patient's extrapyramidal symptoms. Subsequent treatment with anticholinergic agents also proved to be ineffective.

On admission to our department the man's neurological examination revealed a severe dystonia, with fixed retrocollis and tortipelvis, dystonia of the lower limbs, and dystonic spasms involving the axis (BFMDRS Score 70).

In both of these patients, a genetic analysis positively ruled out the presence of a mutation of the *DYT1* gene and a neuroimaging examination, which included MR imaging, yielded normal findings.

*Surgical Technique*

The bilateral ventroposterolateral portion of the GPI was the target for surgery in both of these patients. In each, a preoperative MR imaging examination was performed using a 0.5-tesla unit (Gyrosan T5-NT; Philips Medical Systems, Best, The Netherlands) to determine the intercommissural plane, the midcommissural point, and the anatomical location of the GPI. Axial MR imaging studies included inversion-recovery images registered on the intercommissural plane by using the following parameters: slice thickness 2 mm, gap 0, TR 2000 msec, TE 13 msec, TI 350 msec, turbo factor 9, FOV 260, rectangular FOV 100%, matrix size 256 × 256 (scan percentage 100%), and imaging time 15.36 minutes for 80 slices.

After general anesthesia had been induced in each patient, a head frame (Leksell G; Elekta Instruments AB, Stockholm, Sweden) was tilted in the sagittal plane to the approximate AC-PC plane. A preoperative CT examination was obtained using a volumetric technique with a slice thickness of 2 mm and a gantry angle of 0°. Magnetic resonance images were fused with CT scans obtained under stereotactic conditions through an ad hoc workstation and software (Sofamor Danek Stealth Station, Frame-link 4.0; Medtronic, Inc., Memphis, TN) that provided stereotactic coordinates of the three-dimensional virtually built space. The following coordinates were used for pallidal targeting: 3 mm anterior to the midpoint of the AC-PC line, 20 mm lateral to the midline, and 6 mm below the intercommissural plane. In both patients these coordinates were used to identify a point that appeared to be in the GPI on the fused MR images.

A rigid cannula was inserted through a precoronal para-

median burr hole up to 10 mm from the target. A quadri-polar DBS electrode (DBS-3389; Medtronic, Inc., Minneapolis, MN) was then inserted into the ventroposterolateral portion of the GPI and secured in the burr hole by using a flange (Ethicon Bioplate Co., J&J, Raynham, MA). The procedure was performed on both sides. After the findings on a CT scan ruled out surgical complications (malpositioning included, Fig. 2), and during the same surgical session, electrodes were connected to a pulse generator (Solettra; Medtronic, Inc.). A postoperative MR imaging examination was used to control the electrode positioning in both patients before starting stimulation.<sup>12</sup> This included axial fluid-attenuated inversion-recovery images, sagittal T<sub>1</sub>-weighted images, and axial and coronal T<sub>1</sub>-weighted fast-field echo three-dimensional images. The parameters of these last volumetric sequences were as follows: slice thickness 2 mm, gap 0, TR 30 msec, TE 4.6 msec, flip angle 30°, FOV 220, rectangular FOV 100%, matrix size 256 × 256 (scan percentage 100%), and imaging time 14.43 minutes for 90 slices.

*Results of DBS*

Stimulation was begun on the 1st day after surgery. In accordance with the standard practice used within our neurosurgical group, unipolar stimulation was used at all times and in both patients, with the more distal contact serving as the active electrical site. The following initial settings were used as our stimulation parameters: amplitude 1 V, pulse width 90 μsec, and frequency 130 Hz. These parameters were maintained throughout the initial postoperative treatment as well as during the follow-up sessions.

*Case 1.* After 3 days of bilateral GPI stimulation a neurological examination revealed the presence of a mild trunk dystonia that was evident only during walking. There were no dystonic postures and no dystonic movements of limbs and neck were observed (BFMDRS Score 5).

*Case 2.* After 2 days of bilateral GPI stimulation there was no evidence of any dystonic spasms. After 5 days of stimulation all of the neck and trunk dystonia was completely resolved (BFMDRS<sup>4</sup> Score 8).

These clinical results are described and summarized using the BFMDRS<sup>4</sup> in Table 1. The follow-up period for both cases was 1 year.

**Discussion**

Tardive dystonia affects approximately 15% of patients

who are treated with long-term neuroleptic drug therapy. The symptoms have the potential of becoming irreversible and untreatable in 1 to 4% of these patients.<sup>6,27</sup> A higher incidence has been confirmed in younger patients by a large series of reports and the time lapse from the onset of dystonia to diagnosis has been reported to be approximately 2 years.<sup>15,38</sup> This delay is most commonly due to mistakes in differential diagnoses. At their onset, the dystonic postures and dystonic movements are usually slight and can often be attributed to conversion disorders or hysteria. In Case 1, the initial symptoms of a slight trunk dystonia and cough that increased with both anxiety and walking was originally diagnosed in psychotic terms.

Movement disorders that characterize tardive dystonia do not differ from those observed in other types of dystonia, and it is possible to observe focal, segmental, or generalized forms.<sup>3</sup> Cervical muscles are involved in two thirds of these cases<sup>25,29</sup> and, as we observed in Case 2, torticollis or retrocollis can severely affect the patient's gait (Fig. 2). Focal tardive dystonia generally involves the face or neck, and it typically presents as blepharospasm, oromandibular dystonia, platysmal contractions, involuntary tongue protrusion, laryngospasm, and spasmodic dysphonia.<sup>1,24,31,37</sup> Tardive dystonia can also cause physical and emotional disabilities that have been reported to be associated with varying degrees of depression and/or an exacerbation of psychotic symptoms.<sup>13</sup>

Treatment of tardive dystonia can often be quite challenging. An improvement in response to tetrabenazine has been reported in 68% of cases,<sup>3</sup> and comparable results have been described with regimens of dopamine agonists and anticholinergic and cholinomimetic agents.<sup>22</sup> Atypical neuroleptics seem to improve tardive dystonia, and olanzapine and clozapine are currently the drugs of choice for the condition, although cases of complete or partial treatment failure have been reported.<sup>5,20,21</sup>

Surgical options for drug-resistant dystonia include thalamotomy, pallidotomy, and, more recently, high-frequency DBS. Thalamotomy has been performed with good results, although at times these results have been transient. Side effects following bilateral thalamotomy of dysarthria, dysphonia, and motor disturbances have been reported.<sup>2</sup> In more recent years pallidotomy has been found to achieve better results with less frequent side effects.<sup>28,41</sup> In the last 10 years, DBS has been increasingly used to treat dystonia. Although its mechanism of action continues to be debated, an inhibitory mechanism seems to be responsible for most of the effects of high-frequency stimulation. The GPI is considered to be the target of choice for dystonia. The greatest benefit has been observed in patients with primary dystonia and status dystonicus,<sup>7</sup> although significant improvements have also been observed in patients with symptomatic dystonia.<sup>35,40</sup> In a DBS series of 16 patients with primary dystonia (seven with *DYT1*-positive dystonia) described by Coubes and associates,<sup>8</sup> a mean improvement of 81.3% was found, with a higher mean value (90%) for patients carrying the mutant *DYT1* gene. Symptomatic dystonia seems to be less sensitive to this procedure, with a mean improvement of 45%. Deep brain stimulation is particularly effective on trunk and limb dystonic postures and movements. Torticollis and retrocollis are also sensitive to this procedure, whereas oromandibular dystonia and fixed dystonic postures seem to be modified to a lesser extent.

As far as the surgical treatment of drug-resistant tardive dystonia is concerned, there have been several reports.<sup>28</sup> A complete and stable control of dystonic symptoms was found to occur in one patient with generalized and drug-resistant tardive dystonia, after a right ventral-medial thalamotomy.<sup>17</sup> Two cases of bilateral posteroventral pallidotomies for severe generalized tardive dystonia have been reported by Wang, et al.<sup>36</sup> In both of these cases a stable improvement in the dystonic symptoms was obtained. Trottenberg and colleagues<sup>32</sup> were the first to describe a case of tardive dystonia treated with high-frequency DBS. This was done in a 70-year-old woman who presented with a 6-year history of progressive and medically refractory, severe tardive dystonia.<sup>32</sup> She suffered from severe, disabling dystonic movements of her upper limbs with oromandibular dystonia, blepharospasm, and retrocollis. Bilateral stereotactic implantation of DBS electrodes in both the posteroventral GPI and the thalamus (VIM) resulted in a good level of control of movement disorders. Stimulation of the VIM did not seem to provide any additional benefit inasmuch as dystonic postures and movements reappeared several hours after the GPI pacemakers had been switched off. A literature review did not disclose any other case in which DBS was used for tardive dystonia. In the two patients we describe the dystonic pattern differed from those of the patients described by Trottenberg and colleagues.<sup>32</sup> Both of our patients, in fact, were young men with a dystonic involvement of the inferior limbs and the cervical and trunk muscles.

Dystonia generally develops gradually after many years of neuroleptic treatment and persists despite the fact that the causative drug has been discontinued. Clozapine and anticholinergic agents have been generally ineffective. This observation paved the way for the surgical treatment of tardive dystonia with a bilateral GPI stereotactic implant. These strikingly successful findings after just a few days of high-frequency stimulation were wholly unexpected (Fig. 1). The time lapse between the beginning of neurostimulation and the best therapeutic result seem to be highly variable when treating dystonias. In our experience with 22 patients affected by primary (*DYT1*-positive or -negative) and symptomatic dystonia, there was a variation in this time lapse between 1 and 6 months. We have never observed such an early response to DBS as we found in the present two patients. According to the literature, the expected percentage of improvement in different dystonias is 90% in patients with *DYT1*-positive primary dystonia, 70 to 80% in patients with *DYT1*-negative primary dystonia or tardive dystonia,<sup>8</sup> and 40 to 50% in patients with symptomatic dystonia.<sup>23,33</sup>

The pathophysiological basis of tardive dystonia remains obscure and the mechanism of action of GPI DBS is also unclear.<sup>34</sup> Sanghera and associates<sup>30</sup> described different neuronal discharge activities in patients with dystonia; if this is confirmed, the finding of different results in different dystonias would indicate a variable degree of GPI involvement.

## Conclusions

High-frequency long-term GPI stimulation was found to be safe, rapid, and highly effective in two patients with drug-resistant tardive dystonia. If our results can be confirmed in a larger series of patients, GPI stimulation may become an elective choice for the treatment of tardive dystonia.

## Deep brain stimulation for tardive dystonia

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