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

Report of two cases

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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).11,20 Tardive dystonia was first recognized and described in 1982 by Burke, et al.,1 as a chronic 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.1 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%.37 Although exposure to neuroleptics is known to be the most significant prognostic factor,3,10,38 other drugs, such as prochlorperazine, promethazine, metoclopramide, amoxapine, and veralipride, have also been reported to cause this type of dystonia.3,8,14,18,19 The exposure to an antipsychotic medication does not necessarily need to be long38 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.3 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...
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 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

![Image of case 1](image1.png)

![Image of case 2](image2.png)
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<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Suggested Causative Drug</th>
<th>Duration of Disease (yrs)</th>
<th>BFMDRS Preop Score</th>
<th>Clinical Presentation at Surgery</th>
<th>Improvement (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>33, M</td>
<td>haloperidol, pimozide, &amp; risperidone</td>
<td>5</td>
<td>36</td>
<td>generalized dystonia, torticollis, oral mandibular dystonia, trunk, upper limbs, &amp; ft lower-limb dystonia during walking</td>
<td>42</td>
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<td>2</td>
<td>30, M</td>
<td>haloperidol</td>
<td>3</td>
<td>70</td>
<td>generalized dystonia, fixed retrocollis &amp; tortipelvis, dystonia of lower limbs, &amp; dystonic spasms involving the axis</td>
<td>78</td>
</tr>
</tbody>
</table>

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.6,27 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.15,17 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 psychiatric 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.1 Cervical muscles are involved in two thirds of these cases25,34 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.1,2,3,17 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.13

Treatment of tardive dystonia can often be quite challenging. An improvement in response to tetrabenzamine has been reported in 68% of cases,3 and comparable results have been described with regimens of dopamine agonists and anticholinergic and cholinomimetic agents.22 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.2,10,22

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 dystarhythmia, dysphonia, and motor disturbances have been reported.11 In more recent years pallidotomy has been found to achieve better results with less frequent side effects.23,44 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,7 although significant improvements have also been observed in patients with symptomatic dystonia.5,8 In a DBS series of 16 patients with primary dystonia (seven with DYT1-positive dystonia) described by Coubes and associates,8 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.28 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.27 Two cases of bilateral posteroventral pallidotomy for severe generalized tardive dystonia have been reported by Wang, et al.39 In both of these cases a stable improvement in the dystonic symptoms was obtained. Trottenberg and colleagues32 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.32 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.32 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 (DYTI-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, and 40 to 50% in patients with symptomatic dystonia.35,33

The pathophysiological basis of tardive dystonia remains obscure and the mechanism of action of GPI DBS is also unclear.34 Sanghera and associates36 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.
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References

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