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Editor's comment: Tardive dyskinesia (TD) is the potentially disabling consequence of chronic therapy with dopamine receptor blocking compounds. Affected patients suffer from emotional and social distress, pain, and physical impairments. Medical therapies usually provide limited benefit. Therefore, surgical interventions may represent a useful alternative treatment modality. In this paper, Meredith Spindler and her colleagues review the published literature on deep brain stimulation targeting the globus pallidus interna as an optional therapy for TD. They illustrate their review with their own case of an individual with refractory TD who underwent this procedure and achieved sustained benefit lasting 5 years.

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Review

Globus pallidus interna deep brain stimulation for tardive dyskinesia: Case report and review of the literature
[Universally available]

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ABSTRACT

Tardive dyskinesia (TD) can be a disabling condition and is frequently refractory to medical therapy. Over the past decade there have been many reports of TD patients experiencing significant benefit with deep brain stimulation (DBS) of the globus pallidus interna (GPi). The growing literature on this treatment option for TD consists predominantly of case reports and series. The reported benefit ranges widely, but the majority of cases experienced at least a 50% improvement in symptoms. The anatomical distribution of dyskinesias has not clearly influenced outcome, though fixed postures appear less likely to improve than phasic movements. Onset of benefit can be immediate or take months, and benefit is sustained in most cases, for at least 6 months and up to several years. A wide variety of voltages, frequencies, and pulse widths have demonstrated efficacy. A small number of reports which examined psychiatric symptoms before and after surgery did not find any decline, and in some cases revealed improvement in mood. However, these overall positive results should be interpreted with caution, as the majority of reports lacked blinded assessments, control groups, or standardized therapy parameters. Finally, we present an illustrative case of refractory tardive dyskinesia treated with GPi-DBS with 5 years of follow-up and 4 accompanying video segments.

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1. Introduction

Tardive dyskinesia (TD) is a disabling persistent condition that results from use of dopamine receptor blocking agents. Medical management, consisting of benzodiazepines, anticholinergics, muscle relaxants, dopamine depleting agents, and botulinum toxin injections, is often insufficient and fraught with side effects. In the last decade there have been several reported cases of deep brain stimulation (DBS) used to treat TD [1–6], and in particular tardive dystonia [7–23], usually targeting the globus pallidus interna (GPi), which has also been the target used to treat other hyperkinetic movement disorders [24,25]. Cases of successful thalamic or

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subthalamic stimulation have also been reported [1,14], but this review will focus on pallidal stimulation only, as this was used in the vast majority of published cases. With the exception of 3 cases of tardive dystonia which did not respond to GPi-DBS [15,20], the response in these reports has generally been positive, but has also been highly variable with regard to the timing, degree, and duration of improvement. Reasons for this variability are unclear, but are likely related to the heterogeneity of tardive phenomenology, inconsistencies in lead location within the GPi, a wide range of DBS parameters utilized, and differing outcome measures at varying lengths of follow-up.

2. Review of the literature

2.1. Phenomenology

More cases of GPi-DBS treatment of tardive dystonia have been reported (52 cases in 16 articles) than of tardive dyskinesias (14 cases in 5 articles), presumably owing to the success seen with DBS in primary dystonias. Nineteen of the tardive dystonia cases are reported in 9 articles that present series of various types of dystonia, and in these articles criteria for the diagnosis of TD were not presented. In the majority of reports of pure tardive dystonia, the criteria proposed by Adityanjee et al. [26] in 1999 are used for diagnosis, while the remainder use the criteria put forth by Burke et al. in 1982 [27]. Key features of both criteria include the presence of chronic dystonia, a history of anti-psychotic drug use preceding or concurrent with the onset of dystonia, the absence of family history of dystonia, and exclusion of other causes of secondary dystonia [27]. The difference between the two criteria is in the purity of the dystonia symptoms: whereas the Burke criteria stipulate that dystonia must be the primary symptom, Adityanjee et al. propose 4 subtypes depending on the degree of dystonia relative to other movements [26]. Tardive dystonia, using these criteria, is thought to be less common, have a faster onset, and be more painful and distressing than tardive dyskinesias [26].

Despite these distinguishing characteristics, there is considerable overlap of tardive dystonia and dyskinesias, and the distinction is not always clear, especially when there are phasic dystonic movements. The above criteria for tardive dystonia allow for concomitant choreiform dyskinesias; thus some reports of tardive dystonia involve patients who have a mixed movement disorder. Similarly, as the term dyskinesia is often taken to include both dystonia and chorea, most reports of tardive dyskinesias also involve patients with both phenomena. The close examination and classification of phenomenology in tardive syndromes is important as it may influence how patients will respond to GPi-DBS, including timing of onset, degree, and duration of improvement.

2.2. Outcomes

Reported responses of tardive dyskinesia or dystonia to pallidal stimulation are summarized in Table 1. In the 12 patients for whom a Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) total score is reported, the mean improvement is 62%. Of these 12 patients, 67% had >50% improvement, and 50% experienced >75% improvement. In the 42 patients with BFMDRS motor and disability subscores reported, the mean improvements are 71% for the motor score and 65% for the disability score. Motor subscores improved by >50% in 79% of patients, and by >75% in 64% of patients. Disability subscores decreased by >50% in 71% of patients and by >75% in 48% of patients. In the 28 patients for whom an AIMS score is reported, the mean improvement is 69%; 82% of these improved by at least 50%, and 43% improved by >75%. However, it is important to note that none of these reports employed a sham control group and many of the assessments were unblinded.

Several case series have indicated that the response of chorea and dystonia to GPi-DBS is of equal degree. In 2007, Damier et al. published the only prospective trial with blinded assessment of GPi-DBS for tardive dyskinesias [6]. Symptoms were measured using the Extrapyramidal Symptoms Rating Scale (ESRS) and the Abnormal Involuntary Movement Scale (AIMS). The 10 patients enrolled, as a group, had both dystonic and choreiform movements, which responded equally in degree to the DBS, as measured using the dystonia and chorea subscores of the ESRS. The mean total ESRS and AIMS scores at 6 months had declined by 61% (range 44%–75%) and 56% (range 33–69%), respectively. A double-blind evaluation using video recordings at 6 months was also performed, corroborating an improvement, with a mean decrease in ESRS score of 50% (range 30–66%). Similarly, Chang and colleagues reported 4 patients with segmental or generalized dystonia as well as chorea, with a 71% improvement in the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) motor subscore and a 77% decline in the ESRS dyskinesia subscore, suggesting comparable improvement of both phenomena [11]. Trottenberg et al. reported a case series of 5 patients with improvement of both axial phasic dystonic movements and orobuccolingual dyskinesias by 87% using the BFMDRS motor subscore and 78% using the AIMS, though degree of response of each symptom is not reported separately [7]. Individual case reports noted differential response of axial and appendicular dyskinesias to stimulation, but a specific pattern was not consistently reported [2,4,5].

In reports of tardive dystonia without mention of choreiform movements, phasic dystonic movements appear to be more responsive to GPi-DBS than fixed abnormal postures [8,13,23]. In a large case series of 9 patients, Gruber et al. found the degree of motor response to be equal for orobuccolingual, axial, and limb dystonia, with 83%, 68%, and 79% improvements of BFMDRS motor score, disability score, and AIMS score, respectively, at last follow-up [12]. Similarly, Egidi et al. reported 69 patients with dystonia, 32 of whom had secondary dystonia including 5 with tardive dystonia, and found that the anatomical distribution of dystonic symptoms in these patients did not influence benefit [18]. However, Franzini et al. reported 2 patients, with 42% and 78% reductions in the BFMDRS, in whom orobuccolingual dystonia was less responsive than cervical dystonia [8].

2.3. Onset and duration of benefit

The onset of improvement of choreiform dyskinesias and dystonia varies among reports. Two cases of tardive choreiform dyskinesias improved immediately [3,5], including one which improved within 30–60 s of stimulation [5]. The 10 patients involved in Damier's prospective trial had improvement of their choreiform symptoms within days [6], while other cases of chorea improved more gradually, over 3 months [4] or 6 months [2,11]. While many patients with tardive dystonia had gradual improvement over weeks to months [6,9,11], similar to the response seen in primary dystonias, several patients also had unexpected early improvement, within a few days [7–10,12]. Notably, Capelle et al. report improvement of phasic movements within days, and subsequent improvement in tonic postures over weeks to months [10].

In all cases, benefit was sustained at last follow-up. The duration of study was limited to 6 months in Damier's prospective trial of 10 patients. Follow-up of other cases has ranged from 5 months to 80 months (6.7 years). Twenty-two of these have been followed for up to 1.5 years, 21 patients have been followed for more than 2 years, and 2 have been followed for more than 5 years. In most cases no significant change in symptoms was seen during the follow-up period. In a few reports with longer follow-up, the mean improvement continued to increase from early follow-up to last