Movement Disorders
CLINICAL PRACTICE
REVIEW

Deep Brain Stimulation for the Dystonias: Evidence, Knowledge Gaps, and Practical Considerations

*René Reese, MD,[1,2] Jens Volkmann, MD, PhD[2]**

Abstract: **Background:** Deep brain stimulation (DBS) of the globus pallidus internus (GPi-DBS) is among the most effective treatment options for dystonias. Because the term "dystonia" is defined by a characteristic phenomenology of involuntary muscle contractions, which may present with a large clinical and pathogenetic heterogeneity, decision making for or against GPi-DBS can be difficult in individual patients.
Methods: A search of the PubMed database for research and review articles, focused on "deep brain stimulation" and "dystonia" was used to identify clinical trials and to determine current concepts in the surgical management of dystonia. Patient selection in previous studies was recategorized by the authors using the new dystonia classification put forward by a consensus committee of experts in dystonia research. The evidence and knowledge gaps are summarized and commented by the authors taking into account expert opinion and personal clinical experience for providing practical guidance in patient selection for DBS in dystonia.
Results: The literature review shows that pallidal deep brain stimulation is most effective in patients with isolated dystonia irrespective of the underlying etiology. In contrast, patients with combined dystonias are less likely to benefit from DBS, because the associated neurological symptoms (e.g., hypotonia or ataxia), with the exception of myoclonus, do not respond to pallidal neurostimulation.
Conclusions: It is important to recognize the clinical features of dystonia, because the distinction between isolated and combined dystonia syndromes may predict the treatment response to pallidal deep brain stimulation. The aim of this review is to help guide clinicians with advising patients about deep brain stimulation therapy for dystonia and refering appropriate candidates to surgical centers.

Deep brain stimulation (DBS) has become a mainstay in the treatment of severe, medication-refractory dystonias. The therapy is CE (Conformite Europeene) marked in Europe and is approved by the US Food and Drug Administration under a humanitarian device exemption. Several randomized and controlled clinical trials have proven the efficacy and relative safety of pallidal DBS for the treatment of primary segmental and generalized dystonia[1,2] and, more recently, cervical dystonia.[3] However, DBS for the dystonias remains a specialty indication despite these merits and is restricted to expert centers worldwide. For the large group of patients with adult-onset focal dystonias, it is still a last-line therapy and not an established alternative to (albeit unsatisfactory) botulinum toxin treatment. This is even more surprising, because surgical risks are low; and the dystonias are thought to be circuit disorders (often without structural brain abnormality), such that retuning the circuit by neuromodulation therapy might offer a lasting and causal therapeutic approach in contrast to peripheral selective denervation. The concept of operating earlier in the disease for a better functional restoration and prevention of social disability, which is now widely accepted in Parkinson's disease,[4] has not been applied to the dystonias to date; although, from a theoretical point of view, it would make much more sense in a non-neurodegenerative disease. The main reason for this apparent

[1]Department of Neurology, Rostock University Medical Center, Rostock, Germany; [2]Department of Neurology, University Hospital Würzburg, Würzburg, Germany

***Correspondence to:** Dr. Jens Volkmann, Department of Neurology, University Hospital Würzburg, Josef-Schneider-Strasse 11, D-97080 Würzburg, Germany; E-mail: volkmann_j@ukw.de)
Keywords: deep brain stimulation, dystonia, globus pallidus internus, new dystonia classification, patient selection.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 8 March 2017; revised 10 June 2017; accepted 17 June 2017.
Published online 11 August 2017 in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/mdc3.12519

doi:10.1002/mdc3.12519

gap between enthusiastic presentations of spectacular improvements in some patients and the more austere reception of the therapy by general movement disorders neurologists and people with dystonia may be the variability of outcomes, even in experienced centers. Clinical trials have reported a nonresponder rate of approximately 25%,[1,2] which applied to a carefully selected study population deemed to be optimally suited for this therapy. More alarmingly, clear causes could not be identified for these treatment failures, which might be amendable by better guidelines of patient selection, surgical performance, or postoperative management. Hence, an uncertainty is associated with every DBS procedure in dystonia and contrasts unfavorably with the high expectations of each surgical candidate fostered by the infectious media reports about "miracle" cures.

In contrast to Parkinson's disease, the dystonias are a far more heterogenous group of disorders defined by a clinical syndrome rather than a common pathology. Moreover, most dystonias belong to the orphan or rare diseases based on prevalence, which is making it more difficult to define a standard of care compared with other DBS indications. To complete some of the confusion related to DBS in the dystonias, a new classification scheme has recently been introduced by the Dystonia Task Force of the International Parkinson and Movement Disorder Society.[5] This new classification may allow a better characterization of target populations for DBS in the future; however, for the time being, it conflicts with the old (still clinically used) classification schemes and current selection strategies for DBS in clinical practice.

DBS is a complex, interdisciplinary therapy in which problems may occur anywhere along a multistep treatment path, from patient selection, target definition, and accurate lead placement to long-term management, including setting the stimulation parameters and medication adjustments. In contrast to tremor disorders or Parkinson's disease, therapeutic responses are often delayed by days, weeks, or months in dystonia, which is making it difficult to "titrate" the therapy based on clinical feedback in individuals or to assess therapeutic strategies in larger cohorts. Consequently, the therapy is still less standardized compared with other indications of DBS.

In this review, we summarize the current state of knowledge about DBS for the dystonias with a special emphasis on patient selection, expected outcomes, target issues, and postoperative management. The goal is to provide practical guidance on the management of patients who have dystonia using DBS, which will require us to leave the rigid format of an evidence-based review and weave personal experience into the available evidence for the many knowledge gaps in this field that need further research.

The New Dystonia Classification

The term dystonia describes a movement disorder characterized by sustained or intermittent muscle contractions, causing abnormal, often repetitive movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and is associated with overflow muscle activation.[5,6] This clinical phenomenology is encountered in a wide variety of diseases with very heterogeneous etiopathogenesis. The new classification scheme recently proposed by the International Parkinson and Movement Disorders Society approaches the problem of lumping or splitting these disorders by a very pragmatic and clinically oriented 2-axis classification system.[5] Axis I describes the clinical characteristics of the dystonia syndrome based on age of onset (infancy, childhood, adolescence, adulthood), body distribution (focal, segmental, multifocal, generalized, hemidystonia), temporal pattern (persistent, action induced, diurnal, paroxysmal), and associated clinical features (isolated or combined dystonia). Axis II describes the etiology of the disorder (inherited, acquired, or idiopathic), as defined by history and paraclinical evidence of structural brain damage or genetic cause. It avoids the problems associated with the previous terms "primary or secondary dystonias," which force clinicians to provide an etiopathogenetic diagnosis in the many cases of dystonia that remain unclear despite extensive workup and would need to be reclassified when new etiologies (e.g., genes) are discovered. In particular, a premature diagnosis of "secondary" dystonia (e.g., cerebral palsy) could be a lifelong obstacle for therapeutic reconsideration and may prevent access to invasive therapies or special drug treatments which are thought to be less effective for a secondary etiology. The many cases of levodopa (L-dopa)–responsive dystonia misdiagnosed as cerebral palsy provide striking examples.

What Is the Expected Outcome from Pallidal DBS in Idiopathic or Inherited, Isolated Dystonias?

Idiopathic or Inherited, Isolated, Generalized or Segmental Dystonias

The outcome criteria improvement in quality of life, dystonia severity, and depressive symptoms were prospectively evaluated in 22 patients with isolated generalized dystonia who received treatment with bilateral globus pallidus internus (GPi)-DBS using a multicenter, controlled, and observer-blinded design.[7] In the consecutive follow-up visits at 3, 6, and 12 months after continuous bilateral GPi-DBS, dystonia motor symptoms (assessed by the Burke-Fahn-Marsden Dystonia Rating Scale [BFMDRS]) were improved by 47%, 51%, and 55%, respectively. Orofacial and spasmodic dysphonias, however, remained virtually uninfluenced. Motor disability was ameliorated by 34%, 42%, and 44% at 3, 6, and 12 months, respectively (the BFMDRS disability score). The items "general health" and "physical functioning" (from scores on the Medical Outcomes Study 36-item Short Form Health

doi:10.1002/mdc3.12519

Survey [SF-36] quality-of-life measure) revealed significant improvement at the 12-month visit. No changes in neuropsychological functioning or psychiatric symptoms were documented using the appropriate scales. The study did not reveal a superior outcome for patients who carried the *dystonia protein 1 (DYT1)* mutation versus those who suffered from noninherited, isolated, generalized dystonia. In contrast to patients with parkinsonian and tremor who have a rapid reoccurrence of motor symptoms after temporal cessation of DBS therapy, patients in this study still had markedly improved dystonia after 10 hours of stimulation washout at the 3-month visit. Thus, GPi-DBS may induce longer lasting neuroplastic changes in patients with dystonia. An open-label, 3-year follow-up of this study revealed constant improvement in motor symptoms and quality of life, whereas mood and cognition remained unchanged.[8]

The dystonic syndrome in an individual patient is regarded as "segmental" if 2 or more contiguous segments of the body are affected. Segments per definition are the face, cervical region, upper extremities, lower extremities, and trunk. The typical age at onset for segmental dystonia is approximately 30 years, and the leading symptom is torticollis accompanied by either facial dystonia or dystonia of 1 upper extremity or the trunk.

In a German sham-controlled, multicenter, randomized study, 40 patients with isolated segmental or generalized dystonia were implanted with bilateral electrodes in the GPi for DBS therapy.[1] To uncover possible placebo effects of the implantation procedure, all patients were provided with the stimulation system but then randomized to "stimulation ON" or "stimulation OFF" for 3 months. Blinding to the patients was achieved by a postoperative consecutive assessment of acute effects and side effects for each of the 4 stimulation contacts on both electrodes in each patient. Stimulation parameters were then fixed just below the threshold for side effects (such that the patient could not perceive any acute stimulation effect) or stimulation was turned OFF, depending on randomization. Blinding of the examiners was achieved by a video-based evaluation procedure of dystonic symptoms before surgery and after 3 months of either treatment or sham treatment. The BFMDRS demonstrated a greater reduction of dystonic symptoms in the treatment group (-15.8 ± 14.1 vs. -1.4 ± 3.8; $P < 0.001$). All patients were then switched to "stimulation ON"; and, after 6 months, a mean reduction of dystonic symptoms of 48% could be assessed in all of these patients. Cognition remained unaffected, and depressive symptoms and quality of life showed improvement. There was a difference in latency to treatment response ranging from minutes to hours for mobile dystonia compared with weeks or months for tonic postures. The degree of improvement from bilateral GPi-DBS varied greatly and ranged from 25% to greater than 75% at the 6-month evaluation, but a secondary analysis did not reveal any clear patient-related predictor (segmental vs. generalized dystonia, DYT1-positive vs. DYT1-negative).

A cohort of 32 patients from the former study were evaluated 3 and 5 years after surgery and showed a mean improvement of 61% and 58%, respectively (BFMDRS motor score vs. baseline).[2] Thus, patients continuously improved in the long term, and there was a significant improvement comparing 6 months with 3 years of follow-up. However, only the subgroup of generalized dystonias showed this continuous improvement, which might be explained by a higher rate of tonic or even fixed dystonic postures. Adverse events were infrequent and mostly hardware-related. Serious adverse events resulting in hospitalization were more prevalent in patients suffering from generalized dystonias and included problems with breakage of cables or lead dislocation, possibly due to higher mechanical stress on the implants caused by more severe abnormal body movements. Mild-to-moderate dysarthria and re-occurrence of dystonic symptoms were the most common adverse effects (approximately 5%) and usually could be corrected by adaptation of the stimulation parameters. Similar improvements were reported in several open-label studies and in 2 studies with masked-outcome assessments.[9,10]

Conclusion

GPi-DBS is highly effective in the treatment of idiopathic or of inherited, isolated generalized or segmental dystonias, as indicated by 1 randomized and sham-controlled study. Because pharmaceutical options virtually are not available, GPi-DBS should be offered preferably early in the disease course to avoid hindrance in individual private and professional development caused by this debilitating movement disorder.

Idiopathic, Isolated Focal Dystonias

Adult-onset dystonias with a focal phenotype are the most frequent isolated dystonias. With the exception of task-specific dystonias, such as writers' cramp or musician's dystonia, isolated focal dystonias usually present with predominant involvement of axial and, most often, cervical muscles. First-line treatment is the repeated, selective denervation of dystonic muscles by local botulinum toxin injections. This treatment may fail if neutralizing antibodies emerge (a rare cause with modern toxin formulations) or, more frequently, if the dystonic movements are complex and involve too many muscles in an alternating fashion to allow full symptom control by denervation. To date, DBS surgery has been restricted to patients who have failed prior attempts of botulinum toxin therapy.

In 2001, Parkin et al. published a report on 3 patients[11] and, in 2002, Krauss and colleagues prospectively described the clinical outcome of 5 patients who had primary cervical dystonia (PCD) and received bilateral GPi stimulation.[12] Both studies demonstrated a relevant reduction of dystonic symptoms with GPi-DBS. In the latter study, severity of dystonic symptoms, functional disability, and pain were improved by 38%, 54%, and 50%, respectively, based on the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) 3 months after surgery. Symptoms were further improved at 6 months, at 12 months, and at the final follow-up (mean, 20 months). The relatively greatest improvements were reported between preoperative measures and the 3-month visit (all items) and between 3 months and 6 months (severity score). Of note, relatively

doi:10.1002/mdc3.12519

frequent hardware problems were reported, such as cable fractures at the connection between electrode leads and extension to the pulse maker. This is still a problem in mobile dystonia probably because of a greater mechanical impact onto cables and connectors.

In a cohort of 10 patients with PCD who were prospectively assessed at multiple centers in Canada, the clinical effects of bilateral GPi-DBS were rated by blinded observers.[13] Patients improved in their motor impairment (TWSTRS) by 28% after 6 months and by 43% after 12 months of continuous treatment. Disability and pain scores improved by 66% and 64%, respectively; mood was improved by 58% (Beck's Depression Inventory), and quality of life (SF-36) was improved by 24%.

An additional 8 patients with PCD from a single center were prospectively assessed and evaluated in the long-term (up to 48 months of GPi-DBS; mean, 30 months; range, 12–48 months).[14] The TWSTRS motor score was reduced by 50% at the 6-month evaluation and by a median of 73% at the last follow-up. Scores for disability and pain (TWSTRS) and quality of life (SF-36) were likewise improved; the TWSTRS nonmotor scores improved by greater than 90%.

There is 1 randomized, sham-controlled, multicenter trial for bilateral GPi-DBS in PCD with a total follow-up of 6 months.[3] In that trial, 62 patients were implanted with a neurostimulator system and randomly assigned to either active or sham stimulation. A blinded, postoperative review was conducted for each stimulation contact to assess acute therapeutic effects and the threshold for side effects in both the treatment and sham groups. Thereafter, stimulation parameters for chronic stimulation were fixed below the threshold for (capsular) side effects in the treatment group. In the sham group, stimulation remained OFF. After 3 months, the severity of dystonic symptoms was reduced by 26% in the treatment group, as measured by the TWSTRS severity score (the primary endpoint of the study) compared with 6% in the sham group. There was a 3.8-point difference between the groups, which was significant. TWSTRS disability scores and Bain tremor scores also were significantly improved in the neurostimulation group, whereas TWSTRS pain scores and quality of life (Craniocervical Dystonia Questionnaire 24 score) were not different. At the 3-month visit, all patients received programmed stimulation, and a second review of therapeutic efficacy was done after 6 months of active stimulation in all patients. There was only a minor additional effect on dystonia severity from the additional 3 months of neurostimulation in the treatment group, suggesting that most clinical improvement occurred rapidly within the first weeks after initiating stimulation. However, long-term follow-up data are pending. After 6 months of active stimulation, significant improvements compared with presurgical baseline values were documented for TWSTRS severity (28%), disability (46%), and pain scores (51%); Tsui score (57%); Bain tremor score (66%); and global dystonia ratings by patients (49%) or physicians (53%). Beck's Depression Inventory scores were reduced by 20%, and the Craniocervical Dystonia Questionnaire 24 showed a 28% improvement. Items of dementia (Mattis Dementia Rating Scale) were unchanged. The latter was corroborated by 13 of these patients who underwent more elaborate neuropsychological testing before surgery and 12 months after continuous GPi-DBS.[15] In that study, only verbal fluency was mildly impaired after surgery. Hardware-related complications comprised device infection (n = 3), misplacement/dislocation of electrodes (n = 3) or neurostimulator (n = 1), stroke/hemorrhage (n = 1), and seizure (n = 1). Four patients reported pain at the extension cable. The most frequent stimulation-induced side effect was dysarthria (7 patients; 11%), which was directly related to stimulation intensity but could be resolved by reprogramming only in 1 patient. In the other patients, stimulation parameters resulted in a compromise between stimulation-induced, mild dysarthria and the antidystonic effect. De novo hand tremor was reported in 3 patients and could only be resolved in 1 patient by reprogramming. One case of stimulation-induced parkinsonism was also reported.

One open-label study has presented long-term data from patients with PCD, including follow-up examinations beyond 5 years of continuous bilateral GPi-DBS.[16] Therapeutic efficacy was retrospectively assessed using video ratings by 2 experts who were blinded to patients and treatments for the time points "prior to surgery" and at a mean of 7.7 ± 1.9 years (range, 5–10 years) after surgery. There was a 48% improvement in the "severity" TWISTRS subscore.

Although studies in generalized dystonia have usually reported that orofacial symptoms respond less favorably to DBS compared with appendicular or truncal dystonia, individual patients with severe Meige syndrome[17] have undergone surgery with good outcomes. We summarized the long-term outcomes of 12 patients with Meige syndrome from different German centers.[18] Scores on the BFMDRS showed a mean improvement of 45% after 3 to 6 months of continuous GPi-DBS and of 53% at 12 to 78 months. When we analyzed the different items composing the BFMDRS, after 3 to 6 months and at 12 to 78 months, improvements for eyes (38% and 47%, respectively), mouth (50% and 56%, respectively), and speech/swallowing (44% and 64%, respectively) were observed. Again, dysarthria was reported as a side effect when stimulating above the therapeutic threshold. After 2 years, 1 patient reported an infection of the right electrode, which that had to be explanted but could be re-implanted 6 months later.

Dystonic camptocormia is another rare focal, isolated dystonia that is notoriously difficult to treat with selective peripheral denervation and has responded favorably to pallidal DBS. Affected patients suffer from forceful tonic and/or phasic forward bending of the trunk. In a retrospective assessment of 3 patients, a virtually complete cessation of dystonic symptoms could be demonstrated after continuous GPi-DBS for 38, 39, and 45 months in the respective patientsy.[19] No relevant side effects were reported.

Conclusion

Pallidal neurostimulation is effective in isolated cervical dystonia, as indicated by 1 randomized sham-controlled study, 3 observer-blinded studies, and several open-label studies. Surgery

doi:10.1002/mdc3.12519

in an experienced center can be recommended for patients with severe cervical dystonia who have failed on qualified botulinum toxin treatment based on available evidence. Experience in other isolated focal dystonias (Meige syndrome, blepharospasm, truncal dystonia) generally has been favorable, but there are no systematic analyses, and a reporting bias cannot be ruled out. Nevertheless, if patients suffer from severe and disabling forms of isolated focal dystonia that no longer respond to medical treatment or botulinum toxin therapy performed at an experienced center, then the surgical option should be discussed as an alternative.

What Is the Expected Outcome from Pallidal DBS in Acquired Isolated Dystonias?

Tardive Dystonias and Dyskinesias

Tardive dystonia and dyskinesia are relevant side effects of chronic intake of drugs with an antidopaminergic mode of action. They often cause relevant disability and respond poorly to drug treatment[20] compared with acute dystonic reactions after the initiation of antidopaminergic treatment, which are well treated by anticholinergics.

Tardive dystonia is assumed to be a distinct clinical entity[21] with the typical phenotype of an isolated segmental or generalized dystonia, prominently affecting the trunk with spinal retroflexion. Often, the dystonic phenotype is combined with other tardive motor symptoms, namely, chorea, akathisia, or tics, and may be summarized under the term tardive dyskinesia. Pharmacological treatment options are limited because of low efficacy and/or side effects. Anticholinergics often aggravate choreatic movements. Patients who receive treatment with tetrabenazine, which sometimes has good clinical efficacy, need to be carefully monitored for depression and parkinsonism. Typical neuroleptics, which have caused tardive dystonia, should be stopped and replaced by atypical antipsychotics (clozapine, olanzapine, or quetiapine).[22,23] However, the prognosis in terms of a remission or even a reduction in the symptoms of tardive dystonia/dyskinesia remains poor overall, particularly if the condition persists beyond 1 year.

GPi-DBS has been tested as a treatment option in a few patients with tardive dystonia. There is a report of 5 patients who presented with an early and relevant effect after stimulation onset in motor function and disability scores on the BFMDRS.[24] Virtually complete remission of symptoms was reported in 4 of these patients within the first week of GPi-DBS. There was persistent efficacy after 6 months, which also persisted over the long-term (range, 18–80 months; mean ± standard deviation, 41 ± 21 months) in the initial group and in another 4 patients.[25] Motor function and disability scores on the BFMDRS (82% and 71%, respectively) as well as quality of life and mood were improved compared with baseline. Symptoms of the underlying psychiatric disease as well as cognition remained unaffected overall.

Another small group of 10 patients with tardive dystonia who were prospectively recruited for a controlled trial of GPi-DBS with masked-outcome criteria was followed for 6 months.[26] Patients improved by a mean of 61% on the Extrapyramidal Symptoms Rating Scale (range, 44%–75%) and 56% on the Abnormal Involuntary Movement Scale (range, 33%–69%). Again, no change in the underlying disease was reported. The study has been complemented by another 10 patients, and 14 patients from the combined cohort could be followed for 6 to 11 years after surgery.[27] Six patients were excluded from long-term follow-up because of a diagnosis of Huntington's disease (n = 1), death (unknown cause, n = 1; breast cancer, n = 1; 10 and 5 years after surgery, respectively), withdrawal of stimulation (n = 1), and loss to follow-up (n = 2). This long-term evaluation demonstrated stable reductions in motor symptoms (measured with the Extrapyramidal Symptoms Rating Scale and the Abnormal Involuntary Movement Scale) without further improvement from the 3-month evaluation to the last follow-up. Notably, 1 year after surgery, subscores on the Extrapyramidal Symptoms Rating Scale (namely, parkinsonism, dystonia, and chorea) also were significantly improved compared with preoperative subscores. Psychiatric complaints were reported in 8 patients during 1-year follow-up (depression, anxiety, mania, agitation) and could be resolved by adaptation of psychiatric medication. In contrast, relevant improvement of mood could be demonstrated in 11 of 16 patients, as evaluated with a standardized depression scale (Montgomery-Asberg Depression Scale).

Conclusion

The severity of symptoms in tardive dystonia and dyskinesias and the limited conservative treatment options may advocate for GPi-DBS in individual cases. Patients should be evaluated and treated in a movement disorders center experienced with this exceptional group of patients, offering a multidisciplinary team comprising a stereotactic neurosurgeon, a movement disorders neurologist, and a psychiatrist. To further validate clinical efficacy and safety, larger controlled trials are required.

What Is the Expected Outcome from Pallidal DBS in Combined Dystonias?

The term "combined dystonia" comprises different disorders with a combined phenotype of dystonia and, e.g., myoclonus, parkinsonism, hypotonia, chorea, or ataxia. There are numerous case reports of DBS in this heterogenous group but only few systematic studies. Below, we focus on those disorders for which some evidence from clinical studies is available.

doi:10.1002/mdc3.12519

Inherited Combined Myoclonus-dystonia Syndrome

An *ε-sarcoglycan mutation (DYT11)* is the cause for about 50% of patients with myoclonus dystonia (MD). Intrinsic to the disease, symptoms of myoclonus are sensitive to alcohol, whereas dystonic features (mostly neck and arm) are not. Five patients with classical MD were evaluated after 6 to 9 months of continuous GPi-DBS and had relevant improvements in both myoclonus (87%; Unified Myoclonus Rating Scale) and dystonia (85%; BFMDRS).[28] Patients were followed for a total of 18 months with stable effects. No adverse events were reported.

Because the question of the ideal target is still not answered, combined targeting of the thalamus (nucleus ventrointermedius [VIM]) and GPi has been conducted in a prospective evaluation of 8 patients with MD.[29] Those patients were followed for a mean of 62 months (range, 1–108 months) and showed an approximately 60% improvement in myoclonus and a 50% improvement in dystonic symptoms. The authors reported a higher prevalence of side effects caused by VIM-DBS (dysarthria and worsening of dystonia). Nevertheless, both VIM-DBS and GPi-DBS may reduce symptoms similarly according to the appropriate scales (BFMDRS, Tsui Scale, Unified Myoclonus Rating Scale). At the last follow-up (range, 1–128 months), 1 patient was receiving VIM stimulation only, 3 were receiving a combined stimulation regime, and 3 were receiving GPi stimulation only.

Conclusion

Because of the low number of cases, there is still uncertainty about DBS for patients with MD. In particular, the questions of the ideal target and whether there is an advantage to simultaneously stimulating the thalamus and the GPi are not clear.

Acquired Combined Dystonias

Dystonias resulting from traumatic injuries to the brain, hypoxia or systemic metabolic causes (e.g., neurodegeneration with brain iron accumulation [NBIA] or Wilson's disease) are summarized under the term "acquired dystonia." Data on GPi-DBS in acquired combined dystonias are scarce, and reports are often on single patients or small patient groups. Here, we focus on perinatal hypoxia (cerebral palsy) and NBIA, a heredodegenerative disorder.

Perinatal hypoxia mainly affects the basal ganglia because of their high sensitivity to oxygen debt. The resulting clinical syndrome is summarized under the term "cerebral palsy" and consists of dystonia and choreoathetosis in an individual proportion. Moreover, spasticity and ataxia/hypotonia can be among the clinical spectrum, depending on the extent of brain damage. Higher brain functions characteristically are not affected. For isolated dystonias, pharmacological treatment is usually ineffective.

The clinical efficacy of GPi-DBS for cerebral palsy has been prospectively investigated in 13 adults.[30] The selected group of patients suffered predominantly from dystonia and choreoathetosis with little spasticity or ataxia. Cognitive function was within normal range, and the patients had no substantial structural injury to the basal ganglia, as determined by magnetic resonance imaging (MRI). Motor function improved after 12 months of GPi-DBS by 24% (BFMDRS) compared with baseline. Of note, individual changes in BFMDRS showed a great range from −7.5% (worsening) to +55% (improvement), even in this clinically very homogeneous and dystonia-dominated group of patients.

A heterogeneous group of disorders is summarized under the term "NBIA," all of which share the common pathology of intracellular and extracellular brain iron accumulation resulting in cellular and axonal degeneration with consecutive loss of neuronal function. More than one-half of the affected patients carry mutations in the *PANK2 gene*, which codes for the enzyme pantothenate kinase 2. The pathognomonic imaging correlate is a pallidal hypointensity with a central hyperintensity (on T2-weighted magnetic resonance images), known as "eye of the tiger."[31]

A multicenter, retrospective assessment of clinical results from GPi-DBS in NBIA collected 23 patients, of whom approximately 61% had a mutation in the *PANK gene*. All patients had the "eye-of-the-tiger" sign on MRI. Early improvement (range, 2–6 months after surgery) was 28.5% (mean BFMDRS score compared with baseline), and the improvement was 25.7% at 9 to 15 months.[32] Improvement of dystonia and disability by greater than 20% was observed in 66.7% and 31.3% of patients, respectively. In contrast, caregivers rated quality of life as improved by an average of 83%. A combination of the factors "disease duration" and "preoperative dystonia severity" predicted an improvement in dystonia after 2 to 6 months of continuous GPi-DBS.

Conclusion

GPi-DBS is far from clinical routine in patients with acquired combined dystonias, in which its clinical efficacy is less predictable than that in those with idiopathic or inherited dystonias. Patients with acquired dystonias may be appropriate candidates for GPi-DBS when dystonia is the most debilitating movement disorder of the clinical syndrome and target structures for DBS lack a structural pathology on MRI. In case of a lesioned pallidum, the subthalamic nucleus or the anterior ventrolateral thalamic nucleus (VLa) have been targeted with variable success in individual patients. The differential indication and efficacy need to be explored in larger series.

Current Controversies in Dystonia Surgery

The success of DBS surgery critically depends on the preoperative selection of appropriate candidates and stimulation of a

doi:10.1002/mdc3.12519

defined target volume, which depends on correct positioning of the electrode and optimal parameter settings. However, the ideal target within the GPi to treat dystonia by DBS is still debated. The "motor part" of the GPi corresponds to the posteroventral lateral portion, and this region was more effective for dystonia reduction compared with anterodorsally positioned electrodes.[33] The proximity of the optimal stimulation volume to the internal capsule (running medial and posterior to the GPi) is challenging, because excessive current spread into corticospinal or corticobulbar fibers will cause motor side effects (e.g., impaired fine motor skills) or dysarthria.[34] Mild bradykinesia, gait freezing, and even a full parkinsonian triad have been described in individual patients treated with bilateral pallidal stimulation for dystonia.[3,16,35–40] It is not clear whether patient-related factors or a specific electrode position predisposes patients to these adverse effects.

To avoid stimulation-induced parkinsonism, and also driven by the observation of effects on dystonia in patients with Parkinson's disease who are off L-dopa,[41] the subthalamic nucleus (STN) has been prospectively evaluated as a possible alternative target structure for DBS in dystonia. Clinical effects have been published in 4 patients with segmental and generalized isolated dystonias[42] and in 9 patients with isolated cervical dystonia.[43] Both series showed relevant improvements in motor functions with a follow-up of 1 year. Similar to GPi-DBS, quality-of-life scores (SF-36) were improved (mental subscores), and neuropsychological functions remained unaffected. Compared with GPi-DBS, the spectrum of side effects was different after STN-DBS.[43] Most patients suffered from (transient) dyskinesia, relevant weight gain was observed in 4 patients, and mood problems with (transient) depression occurred in 5 of the 9 patients. The cohort published by Ostrem et al. in 2011 has been further complemented, and 20 patients (12 with cranial/cervical dystonia, 4 with segmental dystonia, 2 with bi-brachial dystonia, and 1 with generalized dystonia) were followed for 1 year.[44] Of these, 14 patients complemented a 36-month visit and, apart from 2 nonresponders (with bi-brachial and cranial/cervical dystonia; 2 of 20 patients; 10%), showed improvements of 70% (BFMDRS motor score) and 67% (TWSTRS total score). There was no difference between improvements at 6 months or at 36 months compared with preoperative scores.

There has been 1 single-center, prospective, double-blind, crossover study comparing the efficacy of GPi-DBS and STN-DBS for the treatment of isolated dystonias. Patients were implanted with bilateral STN and GPi electrodes and randomized to receive stimulation of either nucleus for 6 months, followed by another 6 months of stimulation of the other nucleus. Although no superiority in clinical efficacy was demonstrated between the 2 nuclei, patients who received STN stimulation scored slightly better than those who received GPi stimulation (BFMDRS motor score improvement, 13.8% vs. 9.1%). Five of 12 patients did not accept GPi stimulation for the entire 6 months because of missing effects of GPi-DBS or worsening of dystonia compared with STN-DBS. These data suggest that the STN is a promising target for treating dystonia with DBS, producing motor improvements similar to those achieved with GPi-DBS, mostly transient stimulation-induced side effects, and potentially less primary nonresponders.

Pragmatic Recommendations for Patient Selection and Referral

Decision making for or against DBS in an individual patient is the final part of a complex, multidisciplinary patient assessment. It is important to communicate with the patient and caregivers about realistic treatment goals and the individual surgical and device-related risks. There is a need to define the individual clinical syndrome, its composite of disabilities, and the relative proportion of symptoms to the resulting disability. This may help, within limits, to predict the individual response profile to GPi-DBS.[45]

However, many patients who could potentially benefit from surgery may not get access to an expert selection process at a DBS center, because they are not aware of the option themselves or their treating neurologists may not consider them candidates. The new dystonia classification has important implications in this regard: many general neurologists were insecure about which patients should be sent to an implant center for presurgical workup, because very heterogenous outcomes were reported within and between the different "primary or secondary" dystonia syndromes. For example, patients with "primary" generalized dystonia associated with a DYT1 mutation were thought to respond more favorably than those with a DYT6 mutation and that patients with tardive dystonia (of "secondary" origin) responded better than some patients with "idiopathic primary dystonia" or "heredodegenerative dystonias," such as a pantothenate kinase (PANK) mutation. These considerations have been confusing for nonspecialists and did not support pragmatic clinical decision making. The new classification instead allows the definition of *a clinical syndrome*, which is likely to respond to DBS irrespective of the underlying etiology.

Based on clinical experience, patients with isolated dystonia predominantly affecting the limbs, neck, and trunk are usually good candidates for surgery. This would encompass patients suffering from inherited dystonia, such as *DYT1*, idiopathic segmental, and generalized dystonia, or acquired dystonias, such as tardive dystonia. Additional orofacial involvement (e.g., *DYT6*) leads to less predictable outcomes in this domain[46,47] (which should to be discussed with the patient), but good outcomes can be observed in other body regions. The threshold for referring patients with isolated dystonia syndromes for a consultation at a DBS center should be low if the patient is suffering from functional impairment or social disability. A further etiological workup and an individual risk-benefit analysis can be provided by the expert center but would no longer be required at the level of the referral neurologists.

doi:10.1002/mdc3.12519

In contrast, patients with combined dystonias are less likely to benefit from DBS, because the associated neurological symptoms (e.g., hypotonia or ataxia), with the exception of myoclonus, do not respond to pallidal neurostimulation. From this large group of patients, only those who have dystonia as the predominant feature with a severity of that justifies surgery as a palliative treatment should be referred to DBS centers for presurgical workup outside of clinical trials. This clinical judgement may change if better outcome predictors have been defined in the ongoing clinical studies for secondary dystonias, such as cerebral palsy.

Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

RR: 1A, 1B, 1C, 3A

JV: 1A, 1B, 1C, 3B

Disclosures

Ethical Compliance Statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflict of Interest: Jens Volkmann worked as a consultant for Medtronic, Boston Scientific, AbbVie and Bial; received grants and research support from Medtronic and Boston Scientific; and received honoraria from Medtronic, Boston Scientific, AbbVie, Bial, Allergan, and UCB. René Reese received travel grants from Medtronic and AbbVie.

Financial Disclosures for the previous 12 months: Jens Volkmann worked as a consultant for Medtronic, Boston Scientific, AbbVie, and Bial; received grants and research support from Medtronic and Boston Scientific; and received honoraria from Medtronic, Boston Scientific, AbbVie, Bial, Allergan, and UCB. René Reese received a travel grant from AbbVie.

References

1. Kupsch A, Benecke R, Muller J, et al. Pallidal deep-brain stimulation in primary generalized or segmental dystonia. *N Engl J Med* 2006;355:1978–1990.
2. Volkmann J, Wolters A, Kupsch A, et al. Pallidal deep brain stimulation in patients with primary generalised or segmental dystonia: 5-year follow-up of a randomised trial. *Lancet Neurol* 2012;11:1029–1038.
3. Volkmann J, Mueller J, Deuschl G, et al. Pallidal neurostimulation in patients with medication-refractory cervical dystonia: a randomised, sham-controlled trial. *Lancet Neurol* 2014;13:875–884.
4. Schuepbach WM, Rau J, Knudsen K, et al. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med* 2013;368:610–622.
5. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. *Mov Disord* 2013;28:863–873.
6. Fahn S, Bressman SB, Marsden CD. Classification of dystonia. *Adv Neurol* 1998;78:1–10.
7. Vidailhet M, Vercueil L, Houeto JL, et al. Bilateral deep-brain stimulation of the globus pallidus in primary generalized dystonia. *N Engl J Med* 2005;352:459–467.
8. Vidailhet M, Vercueil L, Houeto JL, et al. Bilateral, pallidal, deep-brain stimulation in primary generalised dystonia: a prospective 3 year follow-up study. *Lancet Neurol* 2007;6:223–229.
9. Sensi M, Cavallo MA, Quatrale R, et al. Pallidal stimulation for segmental dystonia: long term follow up of 11 consecutive patients. *Mov Disord* 2009;24:1829–1835.
10. Valldeoriola F, Regidor I, Minguez-Castellanos A, et al. Efficacy and safety of pallidal stimulation in primary dystonia: results of the Spanish multicentric study. *J Neurol Neurosurg Psychiatry* 2010;81:65–69.
11. Parkin S, Aziz T, Gregory R, Bain P. Bilateral internal globus pallidus stimulation for the treatment of spasmodic torticollis. *Mov Disord* 2001;16:489–493.
12. Krauss JK, Loher TJ, Pohle T, Weber S, Taub E, Barlocher CB, Burgunder JM. Pallidal deep brain stimulation in patients with cervical dystonia and severe cervical dyskinesias with cervical myelopathy. *J Neurol Neurosurg Psychiatry* 2002;72:249–256.
13. Kiss ZH, Doig-Beyaert K, Eliasziw M, et al. The Canadian multicentre study of deep brain stimulation for cervical dystonia. *Brain* 2007;130(pt 11):2879–2886.
14. Skogseid IM, Ramm-Pettersen J, Volkmann J, Kerty E, Dietrichs E, Roste GK. Good long-term efficacy of pallidal stimulation in cervical dystonia: a prospective, observer-blinded study. *Eur J Neurol* 2012;19:610–615.
15. Dinkelbach L, Mueller J, Poewe W, Hodaie M, Poon YY, Fallis M, Moro E. Cognitive outcome of pallidal deep brain stimulation for primary cervical dystonia: one year follow up results of a prospective multicenter trial. *Parkinsonism Relat Disord* 2015;21:976–980.
16. Walsh RA, Sidiropoulos C, Lozano AM, et al. Bilateral pallidal stimulation in cervical dystonia: blinded evidence of benefit beyond 5 years. *Brain* 2013;136(pt 3):761–769.
17. Tolosa ES, Klawans HL. Meiges disease: a clinical form of facial convulsion, bilateral and medial. *Arch Neurol* 1979;36:635–637.
18. Reese R, Gruber D, Schoenecker T, et al. Long-term clinical outcome in Meige syndrome treated with internal pallidum deep brain stimulation. *Mov Disord* 2011;26:691–698.
19. Reese R, Knudsen K, Falk D, Mehdorn HM, Deuschl G, Volkmann J. Motor outcome of dystonic camptocormia treated with pallidal neurostimulation. *Parkinsonism Relat Disord* 2014;20:176–179.
20. Burke RE, Fahn S, Jankovic J, Marsden CD, Lang AE, Gollomp S, Ilson J. Tardive dystonia: late-onset and persistent dystonia caused by antipsychotic drugs. *Neurology* 1982;32:1335–1346.
21. Adityanjee, Aderibigbe YA, Jampala VC, Mathews T. The current status of tardive dystonia. *Biol Psychiatry* 1999;45:715–730.
22. Gourzis P, Skokou M, Soubasi E, Katrivanou A, Polychronopoulos P. Treatment of tardive dystonia induced by antipsychotics, old and New. *Clin Neuropharmacol* 2015;38:121–126.
23. Pinninti NR, Faden J, Adityanjee A. Are second-generation antipsychotics useful in tardive dystonia? *Clin Neuropharmacol* 2015;38:183–197.
24. Trottenberg T, Volkmann J, Deuschl G, et al. Treatment of severe tardive dystonia with pallidal deep brain stimulation. *Neurology* 2005;64:344–346.
25. Gruber D, Trottenberg T, Kivi A, et al. Long-term effects of pallidal deep brain stimulation in tardive dystonia. *Neurology* 2009;73:53–58.
26. Damier P, Thobois S, Witjas T, et al. Bilateral deep brain stimulation of the globus pallidus to treat tardive dyskinesia. *Arch Gen Psychiatry* 2007;64:170–176.
27. Pouclet-Courtemanche H, Rouaud T, Thobois S, et al. Long-term efficacy and tolerability of bilateral pallidal stimulation to treat tardive dyskinesia. *Neurology* 2016;86:651–659.
28. Azoulay-Zyss J, Roze E, Welter ML, et al. Bilateral deep brain stimulation of the pallidum for myoclonus-dystonia due to epsilon-sarcoglycan mutations: a pilot study. *Arch Neurol* 2011;68:94–98.
29. Gruber D, Kuhn AA, Schoenecker T, et al. Pallidal and thalamic deep brain stimulation in myoclonus-dystonia. *Mov Disord* 2010;25:1733–1743.
30. Vidailhet M, Yelnik J, Lagrange C, et al. Bilateral pallidal deep brain stimulation for the treatment of patients with dystonia-choreoathetosis cerebral palsy: a prospective pilot study. *Lancet Neurol* 2009;8:709–717.

doi:10.1002/mdc3.12519

31. Hayflick SJ, Westaway SK, Levinson B, Zhou B, Johnson MA, Ching KH, Gitschier J. Genetic, clinical, and radiographic delineation of Hallervorden-Spatz syndrome. *N Engl J Med* 2003;348:33–40.

32. Timmermann L, Pauls KA, Wieland K, et al. Dystonia in neurodegeneration with brain iron accumulation: outcome of bilateral pallidal stimulation. *Brain* 2010;133(pt 3):701–712.

33. Tisch S, Zrinzo L, Limousin P, Bhatia KP, Quinn N, Ashkan K, Hariz M. Effect of electrode contact location on clinical efficacy of pallidal deep brain stimulation in primary generalised dystonia. *J Neurol Neurosurg Psychiatry* 2007;78:1314–1319.

34. Reese R, Reich MM, Falk D, Deuschl G, Mehdorn HM, Volkmann J. Intraoperative thresholds for capsular stimulation are reliable for chronic pallidal deep brain stimulation in dystonia. *Stereotact Funct Neurosurg* 2017;95:79–85.

35. Berman BD, Starr PA, Marks WJ Jr, Ostrem JL. Induction of bradykinesia with pallidal deep brain stimulation in patients with cranial-cervical dystonia. *Stereotact Funct Neurosurg* 2009;87:37–44.

36. Blahak C, Capelle HH, Baezner H, Kinfe TM, Hennerici MG, Krauss JK. Micrographia induced by pallidal DBS for segmental dystonia: a subtle sign of hypokinesia? *J Neural Transm* 2011;118:549–553.

37. Schrader C, Capelle HH, Kinfe TM, et al. Pallidal deep brain stimulation may induce freezing of gait in patients with focal and segmental dystonia. *Mov Disord* 2010;25(suppl 1):S466–S467.

38. Ostrem JL, Marks WJ Jr, Volz MM, Heath SL, Starr PA. Pallidal deep brain stimulation in patients with cranial-cervical dystonia (Meige syndrome). *Mov Disord* 2007;22:1885–1891.

39. Reese R, Fasano A, Knudsen K, et al. Full parkinsonian triad induced by pallidal high-frequency stimulation in cervical dystonia. *Mov Disord Clin Pract* 2015;2:99–101.

40. Zauber SE, Watson N, Comella CL, Bakay RA, Metman LV. Stimulation-induced parkinsonism after posteroventral deep brain stimulation of the globus pallidus internus for craniocervical dystonia. *J Neurosurg* 2009;110:229–233.

41. Lyons KE, Pahwa R. Effects of bilateral subthalamic nucleus stimulation on sleep, daytime sleepiness, and early morning dystonia in patients with Parkinson disease. *J Neurosurg* 2006;104:502–505.

42. Kleiner-Fisman G, Liang GS, Moberg PJ, et al. Subthalamic nucleus deep brain stimulation for severe idiopathic dystonia: impact on severity, neuropsychological status, and quality of life. *J Neurosurg* 2007;107:29–36.

43. Ostrem JL, Racine CA, Glass GA, Grace JK, Volz MM, Heath SL, Starr PA. Subthalamic nucleus deep brain stimulation in primary cervical dystonia. *Neurology* 2011;76:870–878.

44. Ostrem JL, San Luciano M, Dodenhoff KA, et al. Subthalamic nucleus deep brain stimulation in isolated dystonia: a 3-year follow-up study. *Neurology* 2017;88:25–35.

45. Volkmann J, Benecke R. Deep brain stimulation for dystonia: patient selection and evaluation. *Mov Disord* 2002;17(suppl 3):S112–S115.

46. Bruggemann N, Kuhn A, Schneider SA, et al. Short- and long-term outcome of chronic pallidal neurostimulation in monogenic isolated dystonia. *Neurology* 2015;84:895–903.

47. Panov F, Tagliati M, Ozelius LJ, et al. Pallidal deep brain stimulation for DYT6 dystonia. *J Neurol Neurosurg Psychiatry* 2012;83:182–187.

doi:10.1002/mdc3.12519