Pallidal deep brain stimulation for longstanding severe generalized dystonia in Hallervorden–Spatz syndrome

Case report

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Generalized dystonia is one of the most disabling movement disorders. Ablative stereotactic surgery such as pallidotomy has been performed for medically refractory dystonia. Recently, deep brain stimulation (DBS) has appeared as an alternative to ablative procedures. Nevertheless, there have been few published reports detailing improvement in dystonia with DBS.

This 36-year-old man with Hallervorden–Spatz syndrome suffered from intractable primary generalized dystonia for 28 years. He was completely dependent for activities of daily living and wheelchair bound because of continuous severe dystonic movements in the face, tongue, neck, trunk, and upper and lower extremities while at rest. The Burke-Fahn-Marsden (BFM) Dystonia Rating Scale score was 112 (maximum 120 points). Bilateral DBS of the globus pallidus internus was performed and resulted in marked improvement in motor functioning and dystonic symptoms with a significant reduction in disability. The BFM score improved to 22.5 points (80% improvement) at 3 months postsurgery and the patient’s dystonia was still well suppressed 1 year after surgery.

Bilateral pallidal stimulation is an effective and safe treatment for intractable generalized dystonia in Hallervorden–Spatz syndrome, even if the disability is severe and longstanding.

KEY WORDS • deep brain stimulation • dystonia • globus pallidus internus • Hallervorden–Spatz syndrome

Dystonia is a clinical syndrome characterized by an involuntary muscle contraction causing a sustained twisted or abnormal posture. In generalized dystonia, symptoms begin in an arm or a leg and advance, spreading to involve the trunk and the rest of the body, and some patients become severely disabled despite medical treatment. Most cases of dystonia occur in the absence of an identified cause or structural lesion in the nervous system, and they are considered to be hereditary and are classified as primary or idiopathic dystonia. Most cases of early-onset primary dystonia are due to a DYT1 gene mutation on the long arm of chromosome 9. In addition, dystonia may occur as a result of Wilson disease, multiple sclerosis, stroke, brain trauma, hypoxia at birth, a side effect of a medication, or Hallervorden–Spatz syndrome (secondary or symptomatic dystonia).

Stereotactic surgery, traditionally consisting of thalamotomy and then pallidotomy, has been performed for medically refractory severe dystonia. Recently, DBS of the GP has emerged as a significant therapeutic alternative in intractable dystonia. In contrast to ablative stereotactic procedures, DBS does not require destructive brain lesions and, therefore, lessens the risk of permanent postoperative neurological deficits. Despite these favorable aspects, however, surgical results of pallidal DBS for generalized dystonia are reported from very few institutions, mainly from outside the US because the Food and Drug Administration has only recently approved DBS for dystonia. We report on the successful DBS treatment of longstanding severe intractable generalized dystonia in a patient with Hallervorden–Spatz syndrome. We believe our experience supports the usefulness of this promising therapy.

Case Report

History. This 36-year-old man presented with a 28-year history of a progressive movement disorder. His symptoms began with abnormal movements involving his neck muscles, which progressed to involve the facial muscles and those of the upper and lower limbs. There was no family history of similar symptoms. His parents are first cousins, and he has three sisters and two brothers, all of whom are healthy. He was the product of a normal spontaneous vaginal delivery and walked at the age of 12 months and talked at the age of 18 months. He attended school until the age of
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10 years, when he stopped because of increasingly abnormal movements. Previous investigations performed in 1993 included karyotyping, hormonal assays, screening for Wilson disease, computerized tomography scans of the brain, and lumbar puncture; all results were negative. At that time, his condition was diagnosed as sporadic dystonia musculorum deformans. He underwent treatments with levodopa and anticholinergic drugs, which were unsuccessful. He also received some injections of botulinum toxin in the affected muscles, which resulted in partial improvement. Despite this, he has experienced progression of his abnormal movements and has become essentially wheelchair bound. He was referred to our institution for possible surgical treatment in 2002.

Examination. On examination, the patient’s vital signs were normal. He could speak, but with severe dysarthria. His overall mental status seemed to be subnormal, although he responded appropriately to simple commands. He had loss of vision in the left eye. He suffered from continuous severe dystonic movements in the face, tongue, neck, trunk, and upper and lower extremities at rest; he could hardly walk with assistance. He displayed generalized rigidity and hyperreflexia; his feet were deformed bilaterally. Continuous dystonic movements of both upper and lower limbs made assessing his power difficult. He was completely dependent on others for activities of daily living and was wheelchair bound. The BFM Dystonia Rating Scale score was 112 (maximum 120 points).

The admission 1.5-tesla T2-weighted MR images demonstrated an area of low signal intensity in the GP consistent with iron deposition and an anteromedial area of high signal intensity (eye-of-the-tiger sign; Fig. 1). Multiple irregular hyperintense lesions indicating ischemia were also demonstrated in the periventricular cerebral white matter and pons. Based on his clinical course and characteristic MR findings, a diagnosis of Hallervorden–Spatz syndrome was made. Implantation of deep brain stimulators into the bilateral GPi was planned for treatment of his disabling severe dystonia.

Operation. The entire surgical procedure was performed after induction of general anesthesia because the patient showed continuous hyperkinetic dystonic movement. Therefore, target localization was based solely on direct visualization on MR images without physiological refinement by intraoperative microelectrode recording. The DBS leads (Activa 3387; Medtronic, Inc., Minneapolis, MN) were implanted at the GPi (posteroventral pallidum) bilaterally. Subsequently, internal pulse generators (Soleta; Medtronic, Inc.) were placed in infraclavicular pockets bilaterally and were subcutaneously connected to the DBS leads.

Postoperative Course. After recovering from anesthesia, the patient showed dystonic movement. The stimulator was adjusted to monopolar stimulation on postoperative Day 1 by using Contact 1 as the negative and the internal pulse generator case as the positive pole with an amplitude of 4 V, a frequency of 185 Hz, and a pulse width of 120 μsec. Postoperative MR imaging demonstrated placement of DBS electrodes at the GPi/GP externus junction (Fig. 2). The actual locations of the active contacts measured using the Stealth system’s Flame Link software (Medtronic, Inc.) were 22.6 mm lateral, 2.9 mm anterior to the PC, and 1.4 mm below the AC–PC line for the left side, and 22.2 mm lateral, 3.4 mm anterior to the PC, and 0.1 mm below the AC–PC line for the right side. Postoperatively, the dystonic movements of the trunk and upper and lower extremities were dramatically extinguished and those in the face, tongue, and neck were well suppressed by activating the DBS. The stimulator was further adjusted to an amplitude of 5 V to obtain maximum effect in the next few weeks. Within 1 week after surgery, the patient began physical therapy in the rehabilitation facility. His activities of daily living scores improved significantly: despite bilateral ankle deformity, he could stand up independently and walk with the aid of a walker at 3 months postsurgery. The BFM Dystonia Rating Scale score at that time was 22.5 points (80% improvement). Subsequently, his dystonia was still well suppressed with the same stimulation parameters at the last follow-up review 1 year after surgery.

Discussion

Hallervorden–Spatz syndrome is a rare, autosomal, recessive neurodegenerative disorder with iron accumulation in the brain as a prominent finding.5,6,17 Clinical features include onset during the 1st two decades of life, a relentlessly progressive course, extrapyramidal dysfunction (dystonia, rigidity, or choreoathetosis). The characteristic MR finding

Fig. 1. Preoperative MR images (fast–spin echo inversion-recovery method, TR 4000/TE 30/TI 180 msec) demonstrating an area of low signal intensity in the GP and an anteromedial area of high signal intensity (eye-of-the-tiger sign).

Fig. 2. Postoperative MR images (axial: spin echo, TR 2500/TE 90 msec; coronal: fast spin echo, TR 3000/TE 96 msec) demonstrating appropriate placement of DBS electrodes in the bilateral GPi.
is the eye-of-the-tiger sign, which is created by a diffuse hypointense signal throughout the GP and hyperintensity in the anteromedial aspects of the GP on T2-weighted images. The hypointensity corresponds to iron deposits in dense tissue, and the hyperintensity of the eye-of-the-tiger sign corresponds to an area of loose tissue with vacuolization.15

Generalized dystonia is one of the most disabling movement disorders. Therefore, surgical treatment may be considered in patients with severe dystonia who have not responded to medical therapy. The fact that “off” dystonia in PD was relieved by pallidotomy led to a resurgence of pallidotomy as a treatment for this condition.18 Ablative stereotactic surgery such as thalamotomy or pallidotomy has been used for a long time in a relatively broad spectrum of patients.7,11–13,18 Justesen, et al.,4 reported successful unilateral pallidotomy and Tsukamoto, et al.,19 reported successful staged bilateral thalamotomy for control of severe dystonia in Hallervorden–Spatz syndrome. Recently, DBS has appeared as an alternative to ablative procedures. Deep brain stimulation seems to reduce the activity of a focal area in a manner similar to ablative surgery by producing a functional lesion in the brain. Compared with ablative surgery, DBS is nondestructive and reversible. Consequently, DBS lessens permanent neurological deficits. Additionally, maximal efficacy with minimal adverse events can be obtained by adjusting the stimulation parameters noninvasively. Although this procedure has been widely applied for the treatment of PD or essential tremor, few data have been published detailing results obtained with DBS in dystonia.3,5,9,10,18,21,23,24

Coubes, et al.,5 reported a mean improvement of 90.3% on the BFM score after bilateral pallidal DBS in seven DYTI-positive patients. Tromnior and Fogel18 reported marked benefit from pallidal DBS in two patients with primary dystonia and some benefit in a patient with postanoxic secondary dystonia. Vercueil, et al.,21 reported a greater benefit of pallidal DBS in a retrospective study of 19 patients treated with thalamic and/or pallidal DBS.21 In general, the best results seem to be obtained in patients with DYTI mutations, and improvement in secondary dystonia was less than for primary dystonia. Accordingly, pallidal DBS has recently been approved for intractable primary dystonia. Very few cases of patients treated for secondary generalized dystonia have been reported. Vercueil, et al., reported on five patients who underwent thalamic DBS for secondary generalized dystonia. They included two with postanoxic dystonia who experienced no improvement, one with postrauamatic dystonia who attained moderate improvement, and two with Hallervorden–Spatz dystonia who had minor and moderate improvements, respectively. On the other hand, Ghika, et al.,6 reported major improvement of postanoxic generalized dystonia after thalamic DBS. Ours is the first reported case of pallidal DBS for dystonia in Hallervorden–Spatz syndrome and our results further support the use of DBS in treating secondary generalized dystonia. The severity (BFM score 112) and longevity (28 years) of dystonia in our patient were unusual compared with other reports. Although pallidal DBS is effective in longstanding severe dystonia, secondary orthopedic deformities persist after surgery. Therefore, much earlier intervention should be considered for severe cases.

The pathophysiological mechanism of DBS of the GPi for dystonia is not well understood. The primary projection from the GPi is inhibitory to the motor thalamus. According to a model of movement disorders, hypokinetic disorders such as PD appear to result from increased mean discharge rates of neurons in the GP, whereas hyperkinetic disorders such as dystonia are associated with decreased mean discharge rates in the GPi.22 Actually, electrophysiological data demonstrated that the firing rate of GPi neurons in a patient with generalized dystonia was lower than that in a patient with PD and in healthy nonhuman primates.12 Therefore, it is reasonable that pallidal DBS that reduces GPi activity is effective for PD. Nevertheless, pallidal DBS is also effective for dystonia. Regarding this contradiction, Vitek, et al.,23 additionally demonstrated changes in the pattern and degree of synchronization of pallidal neurons in dystonia. Excessive reductions in the mean discharge rates of GPi neurons could lead to changes in the pattern and degree of synchronization of thalamic neuronal activity, which may contribute to the development of dystonia. Therefore, DBS of the GPi seems to be effective for dystonia because it removes the source of inhibitory input to the thalamus and normalizes thalamic neuronal activity.23 According to these authors’ theory, thalamic DBS also may be effective. Nevertheless, pallidal DBS seems to be more successful, at least for primary generalized dystonia, than thalamic DBS.21

In our patient, stimulation parameters (amplitude, frequency, and pulse width) were much higher than those in patients with PD. This may be because of the disease’s severity or a different mechanism of inhibition of GPi activity. Generally, it seems that a much longer pulse width is required for dystonia.10 Deep brain stimulation has the potential to increase the intensity of stimulation by allowing modification of parameters to yield a better result. Some authors have reported that the improvement of dystonia was delayed and it took a few months for the full effect to be manifested after pallidotomy or DBS.11,13,18 Benabid, et al.,2 suggested that the improvement in dystonia is a phenomenon of plasticity rather than the simple inhibition of a loop. Our patient showed a significant suppression of dystonic movement immediately after the stimulation began. This may have also resulted from the flexibility of DBS in terms of selecting the location of active contact and changing stimulation parameters.

Conclusions

Bilateral pallidal stimulation is an effective and safe treatment for intractable generalized dystonia characteristic of Hallervorden–Spatz syndrome, even if the condition is severe and longstanding. Early surgery should be considered for severe generalized dystonia to prevent secondary orthopedic deformities.

References

3. Bereznai B, Steude U, Seelos K, et al: Chronic high-frequency globus pallidus internus stimulation in different types of dystonia:
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a clinical, video, and MRI report of six patients presenting with segmental, cervical, and generalized dystonia. Mov Disord 17: 138–144, 2002


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