Pallidal or Subthalamic Deep Brain Stimulation for the Generalized Dystonia Treatment

Tomasz Mandat, Krzysztof Szalecki, Henryk Kozlara, Emilia Soltan, Bartosz Krolicki, Bartosz Czapski, Bogdan Brodacki, Wieslaw Bonicki and Tomasz Kmiec

Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Neurosurgery ul. Roentgena 5, Warszawa, 02-781, Poland

Corresponding author: Tomasz Mandat, Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Warszawa, Poland, Tel: 48225462360; E-mail: tomaszmandat@yahoo.com

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Abstract

One of the most effective treatments of medically refractory generalized dystonia (GD) is pallidal deep brain stimulation (GPI DBS). For selected group of GD patients, subthalamic deep brain stimulation (STN DBS) might be similarly effective. The authors present a group of patients diagnosed with GD, treated with GPI or STN DBS.

Materials and methods: Between 2005 and 2009 eleven female and eight male patients with diagnosed GD were treated with GPI DBS or STN DBS. Mean age at implantation was 26 ± 6. Two patients were diagnosed with DYT-1 mutation. Seven patients were diagnosed with PANK-2 mutation. One patient with previous bilateral pallidotomies and six patients with diagnosed PANK-2 mutation were qualified to STN DBS. Rest of the group was qualified to GPI DBS. Clinical status of the patients was evaluated with a package of dystonia scales. The follow-up evaluation was conducted 60 months after implantation.

Results: The patients reported subjective improvement following surgery that was confirmed with tailored scales. Mean improvement was evaluated with Global Dystonia Scale to 48%. More significant improvement was reported in the GPI group than in the STN group (51% vs. 38%). The best results were achieved in the DYT-1 group (89%).

Conclusion: Although analyzed group is not large, the authors state that deep brain stimulation is effective and safe method of GD treatment. Decision which anatomical target is optimal should be undertaken individually depending on clinical history, phenotype and etiology of GD.

Keywords: Dystonia; Deep brain stimulation; Globus pallidus; Subthalamic nucleus

Introduction

Dystonia is characterized by complex, involuntary, repetitive movements. Mioclonia, tremor, bradykinezia, increased or decreased muscle tone supplements the phenotype of dystonia. The character of abnormal movements includes dynamic or static posture. Depending on range of symptoms, dystonia might be divided in to: focal, segmental and general dystonia (GD). Depending on etiology dystonia can be related to: injury, infection, ischemic or hemorrhagic stroke, metabolic disorders, intoxication or genetic mutation.

Defined etiology of GD can be indicated only among particular cases, and the cause of the symptoms can be cured extremely rarely. The treatment of choice of focal and segmental dystonia remains pharmacotherapy.

Pharmacoresistance or lack of tolerance of the treatment might lead to neuromodulative treatment with ablative procedures or deep brain stimulation (DBS). Reversible mechanism of DBS with lower risk of permanent neurological deficit indicates DBS as preferable. Spectacular improvement after DBS in selected types of genetic mutations favors neurosurgical treatment in those patients [1-13]. Heterogeneity of symptoms and lack of animal model of dystonia are the main reason of absence of qualification algorithm and standardized treatment protocol [2,4,7,9,13].

The authors present a group of medically refractory GD patients treated with pallidal (GPI) or subthalamic (STN) DBS. The aims of the study were to evaluate and compare efficacy and safety of GPI DBS and STN DBS in GD.

Materials and Methods

A group of 11 female and 8 male (mean age 22 ± 6), severely impaired by pharmacologically resistant GD patients were qualified to the surgery. All patients were qualified to the surgery at the movement disorders centers.

All patients underwent neuropsychological evaluation before treatment [14]. DYT-1 mutation was identified in 2 cases. PKAN (pantothenate kinase-associated neurodegeneration)/NBIA1 (neurodegeneration with brain iron accumulation-1) with PANK-2 ( locus 20p13-p12.3 ) mutation was identified in 7 cases. Secondary GD was diagnosed in 4 cases: electric shock at childhood, midbrain and cerebellar ischemic stroke at age of 24 and perinatal injury (2 cases). Primary dystonia was diagnosed in the remaining 6 cases. All patients were qualified for GPI DBS. Because of previous ineffective pallidotomy the surgical target was shifted to STN in one case.

Significant morphological changes of globus pallidus (iron accumulation) confirmed with MRI forced the authors to move the surgical target among 6 patients with PANK-2 mutation to STN. The clinical status of the patients was evaluated with Global Dystonia Scale (GDS), Burke-Fahn-Marsden Movement Scale (BFM) and Unified
Dystonia Rating Scale (UDRS). The patients were admitted to the hospital two days prior surgery. Awake implantation of the DBS was performed in 2 cases. Severe dystonic movements obliged to use general anesthesia during whole procedure in the rest of the group. After application of the stereotactic frame (Leksell, Elekta) and CT, the images were fused (MRI T1 and T2 with stereotactic CT). The target was identified with indirect (mid AC-PC: 3/20/5 for GPi and 2/11/4 for STN) and modified with direct method depending on T2 MRI [9,15].

After shallowing of the sedation microrecording with one to 5 paths was used in 7 cases and macrostimulation was used in all cases [10,16,17]. After identifying of the neurphysiological target the permanent electrodes were implanted under fluoroscopic guidance. The programming of the internal pulse generator started on the first day following surgery. The effectiveness was evaluated with previously mentioned scales 60 months after surgery.

Statistical Analysis

The nominal or measured variables on an ordinal scale are presented in the form of percentages with 95% confidence intervals (95% CI). Due to the nature of the distribution it deviates from the normal qualitative variables and are presented both from the arithmetic mean of the 95% CI and the median of the range of values.

In the comparative analysis of qualitative variables routinely chi-square test was used, and if the expected frequencies were less than 5 exact two-sided Fisher’s test was used. Quantitative variables in the subsequent time points were compared with the Wilcoxon test. Adopted for all tests the level of statistical significance is p<0.05. Statistical calculations were performed using STATISTICA 8.0 PL (StatSoft, Inc. 2008).

Results

All patients reported subjective improvement after surgery, which was verified by listed scales. The initial stimulation parameters were set at: monopolar stimulation (C +, 0-, 1-) 180 Hz frequency, pulse width 450us for GPi and 130 Hz, 90 us for STN with the amplitude of 1.0 V. During follow-up, depending on the beneficial response or adverse effects, the parameters were modified by introducing a bipolar stimulation and increasing the amplitude up to 4.5 V and reducing the frequency to 60 Hz and pulse width to 130 us. The settings of the stimulation remained stable from 12 to 60 months after surgery.

The first evaluation was performed 12 months after surgery and the results remained stable at the 60 months follow-up [18]. At the follow-up the average improvement of 48% was assessed with GDS (Figures 1 and 2 and Tables 1 and 2). Better results were obtained in the GPI DBS group (52%) compared to the STN DBS group (38%). This difference, however, was not statistically significant (p=0.180). The best results were obtained among DYT-1 mutation patients treated with GPi DBS (87%), however, due to small size of the group the difference was not statistically significant (p=0.098).

The poorest results were obtained in a PANK-2 patient treated with GPi DBS (17%, p<0.05). Improvement among a group of patients with primary dystonia was 48.7% (p=0.065) and secondary dystonia group was 48.5% (p<0.05). Reduction of the severity of dystonic movements consisted mainly of the muscles of the face, neck and the proximal muscle groups of extremities. The reduction of the severity of dystonic movements were observed to a lesser extent within the distal muscle groups of the extremities and the trunk. Fixed dystonic postures did not improve.

Figure 1: Mean reduction of dystonia severity measured with percentage of GDS (95%CI) improvement depending on ethiology of dystonia. SD: Secondary Dystonia, PKAN: Pantothenate Kinase-Associated Neurodegeneration, PD: Primary Dystonia, DYT-1: DYT-1 Related Torsion Dystonia.

Figure 2: Severity of dystonia measured with reduction of GDS, BFM and UDRS (95% CL) before surgery (DBS OFF) and with stimulation (DBS ON) depending on the etiology of dystonia and surgical target.
8 months after surgery concurrent dysfunction (high impedance) of two electrodes were found in one GPI DBS case. The patient was treated for severe GD accompanied by torticollis and retrocollis. The clinical condition of the patient has improved significantly after surgery with rapid deterioration 14 months later. X-ray revealed connectors migration to the supraclavicluar region bilaterally. New
system was reimplanted. After surgery and initiation of stimulation, the impedance was normal and the patient’s condition has improved rapidly to the previous state.

10 months after surgery a Gpi DBS patient treated because of GD and torticollis reported with rhythmic neck muscle contractions, which tend to disappear after switching off the IPG. X-ray revealed connector displacement to the retromandibular region. The connector was replaced surgically to the retrosigmoid region and anchored to the fascia. After the surgery motor spasms of the neck muscles vanished. Because of battery depletion all IPGs were exchanged. Mean longevity of the battery (Soletra, Medtronic) were 24, 5 months for Gpi and 38 months for STN.

**Discussion**

Definition of dystonia is set more by a description of symptoms than a description of a single defined disease. Unlike to Parkinson’s disease and MPTPT model, creation of dystonic animal model is very difficult if not impossible to define. The laboratory model of abnormal movements observed in dystonia explains its pathology as a dopaminergic neuronal loop dysfunction. It is believed that similarly to Parkinson’s disease, discart of cortico-basal-thalamo-cortical loop with its direct and indirect connections plays important role in pathophysiology of dystonic movements and explains mechanism of neuromodulative treatment with functional suppression (DBS) or ablation of STN or Gpi [7,9,11,18-23].

Wariness and skeptical approach to neurosurgical treatment of GD is conditioned by the beginnings of functional neurosurgery in the first half of the twentieth century, when the efficacy and safety of neuromodulative treatment of movement disorders were much lower than today. Introduction of DBS in the end of the XX century partially revolutionized this approach [24-28]. The efficacy of dystonia treatment with Gpi DBS at three-year follow-up is estimated at 90% among patients with DYT-1 mutation, 80% with idiopathic GD, and the worst results are obtained among patients with defined secondary dystonia. The positive effect of DBS on GD patient’s quality of life and good tolerance of the treatment have been confirmed in several studies [3,4,23,29-32]. Recent years brought a growing interest in the disease and MPTPT model, creation of dystonic animal model is very difficult if not impossible to define. The laboratory model of abnormal movements observed in dystonia explains its pathology as a dopaminergic neuronal loop dysfunction. It is believed that similarly to Parkinson’s disease, discart of cortico-basal-thalamo-cortical loop with its direct and indirect connections plays important role in pathophysiology of dystonic movements and explains mechanism of neuromodulative treatment with functional suppression (DBS) or ablation of STN or Gpi [7,9,11,18-23].

Poor results of conservative treatment of GD patients should lead to surgical neuromodulative treatment before fixed dystonic posture appeared [33-36]. At the beginning of the qualification process it is necessary to establish realistic treatment goals and mile stones that should be accepted by both patients and their relatives. In addition to typical contraindications for DBS (coagulopathy, uncontrolled hypertension, cerebrovascular disease, psychiatric disorders and terminal condition), the age factor should not be underestimated. Adolescent group of patients with idiopathic dystonia has a tendency for self-limitation (psychogenic puberal dystonia) and the qualification for surgery in this age group should be undertaken extremely carefully. However if PANK-2 or DYT-1 mutation were identified among medically-refractory GD the surgical treatment should be undertaken without hesitance. Rapid development of symptoms among PKAN patients that lead to serious complications and affect their life expectancy force to undertake treatment even in young children [14].

Timing and methodology of postsurgical assessment are crucial for obtained results. Even though multiple scales were introduced for evaluation of dystonia, the complexity of abnormal movements make evaluation not simple. A number of scales used to assess dystonia complement each other and it is difficult to identify the most universal one. Undoubtedly dynamic, dystonic movements tend to respond most rapidly after initiation of stimulation, and the fixed dystonic postures respond slower if respond at all [13,20,22,24]. Commonly observed extreme positions of head and neck among patients with GD and torticollis predispose risk of migration of the connecting wires that leads to damage of especially vulnerable brain electrodes. Special attention should be undertaken for evaluation of the position of the connectors among GD patients [2,4,9,10,29-33].

**Conclusion**

Although the analyzed group in not large, type and range of dystonia are heterogeneous, the authors state that Gpi and STN DBS are similarly in the meaning of safety and effectiveness methods of GD treatment. The main influence on the outcome has the etiology of dystonia. The nature of dystonic movements will affect obtained results of the treatment where the dynamic movements tend to respond quickly to the therapy and fixed dystonic postures tend not to respond at all. The choice of the anatomical target point for DBS should be carried out individually on the basis of previous treatment and clinical picture of dystonia.

**References**


