Parkinsonism and Related Disorders xxx (2017) 1–8

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Long-term follow-up of bilateral subthalamic deep brain stimulation for refractory tardive dystonia

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ARTICLE INFO

Article history:
Received 15 January 2017
Received in revised form
29 April 2017
Accepted 14 May 2017

Keywords:
Antipsychotic
Deep brain stimulation
Dyskinesia
Psychosurgery
Subthalamic nucleus
Tardive dystonia

ABSTRACT

Background: No effective treatment for tardive dystonia (TD) has been well established. Deep brain stimulation (DBS) can ameliorate motor manifestations in primary dystonia, and may also be an effective approach for TD.
Objectives: This study aimed to illuminate the long-term efficacy and safety of subthalamic nucleus (STN)-DBS in treating TD.
Methods: Ten patients with refractory TD underwent STN-DBS therapy and were assessed by the Burke-Fahn-Marsden dystonia rating scale (BFMDRS), Abnormal Involuntary Movement Scale (AIMS), Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), and the Short Form (36) Health Survey (SF-36) at four time points: pre-operation, 1 week post-operation, 6 months post-operation, and at a final long-term postsurgical follow-up time point.
Results: The mean follow-up time was 65.6 ± 30.4 months (range, 12−105 months). At the first follow-up, BFMDRS motor and disability scores had improved by 55.9± 28.3% and 62.6± 32.0%, respectively, while AIMS scores improved by 53.3± 26.7%. At the second follow-up, BFMDRS motor and disability scores improved further, by 87.3± 17.0% and 84.3% ± 22.9%, respectively, while AIMS scores improved by 88.4 ± 16.1%. At the last follow-up, this benefit was sustained and had plateaued. Quality of life was improved significantly at the long-term follow-up, and the HAMA and HAMD scores displayed a significant reduction that persisted after the first follow-up.
Conclusion: STN-DBS may be an effective and acceptable procedure for TD, leading to persistent and significant improvement in both movement and psychiatric symptoms.

1. Introduction

Tardive dystonia (TD) is a disabling and irreversible extrapyramidal movement disorder that is commonly caused by the prolonged intake of dopamine receptor-blocking medications, characterized by stereotypy behaviors and abnormal posture resulting from involuntary sustained muscular contractions. Dystonic symptoms primarily predominate in the axial musculature, including the muscles of the neck, jaw, and trunk [1], which burdens patients and their caregivers. The prevalence of TD is estimated to be 0.4−9% [2].

The medical treatment of TD is challenging; the conventionally administered pharmacotherapies such as, anticholinergics, are only beneficial at the initial stage [3], but lack satisfactory outcomes in the long term [4]. One controlled trial reported that benzodiazepines, namely diazepam and clonazepam, do not demonstrate favorable efficacy [5]. Botulinum toxin injection is a highly effective approach in the treatment of focal dystonia such as cervical dystonia, yet a proportion of patients show low levels of satisfaction after treatment and fail to follow up for repeated treatments [6]. Elderly patients undergoing prolonged treatment with medication are more likely to experience side effects, and persistent dystonic symptoms are significantly associated with high mortality [7]. Thus the pharmacotherapeutic method should be regarded as an

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http://dx.doi.org/10.1016/j.parkreldis.2017.05.010
1353-8020/

adjuvant therapy instead of a priority choice as the disease progresses to the advanced stage. Surgical intervention is a promising method warranting further investigation, particularly deep brain stimulation (DBS) therapy, which has established efficacy for controlling medically refractory dystonia, ameliorating motor function, and improving quality of life (QoL) with long-term results [8–11], and minimal cognitive impairment [12]. The majority of investigations of DBS in patients with TD have focused on internal globus pallidal deep brain stimulation (GPi-DBS), while less is known about subthalamic nucleus deep brain stimulation (STN-DBS), despite its demonstration of more rapid systemic improvement, better systemic control, and longer battery life [13] than GPi-DBS for Parkinson's disease. Sun *et al* [13], reported two patients with TD with significant positive outcomes after undergoing STN-DBS therapy. Recently, a study showed a positive result for a patient who underwent STN-DBS 12 years prior. This patient had a significant improvement in motor function of up to 100% during the DBS-on period and could even perform physical exercises during the DBS-off period [14], However, large sample clinical studies are necessary to explore its efficacy and safety. Here, we retrospectively investigated long-term outcomes in 10 patients with TD in terms of motor function, QoL, and psychiatric state.

2. Methods

Ten consecutive patients (4 women and 6 men) with refractory TD that met the diagnostic criteria described by Adityanjee [15] underwent a bilateral STN-DBS procedure at the Functional Neurosurgical Center of Shanghai Ruijin Hospital from 2008 to 2015. This study was approved by the ethical committee of Ruijin Hospital. All subjects provided written informed consent according to the institutional guidelines for participation and publication.

2.1. Clinical assessment

All patients were diagnosed and evaluated by an experienced neurologist (responsible for the diagnosis and evaluation of TD) and by a professional psychiatrist (responsible for the diagnosis and evaluation of psychiatric disease) pre- and post-surgery. Each of the 10 patients were rigorously assessed by the Burke-Fahn-Marsden dystonia rating scale (BFMDRS), Abnormal Involuntary Movement Scale (AIMS), Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), and the Short Form (36) Health Survey (SF-36) pre-surgery (baseline), 1 week after surgery, 6 months after surgery, and at long-term follow-up (range, 12–105 months) to assess dystonia severity, extrapyramidal symptoms, psychiatric state, and QoL, respectively.

2.2. Surgical procedure

Patients underwent standard stereotactic bilateral STN-DBS implantation procedures after they provided written informed consent. Magnetic resonance imaging (MRI) (1.5 T; General Electric Company; USA) and macro-stimulation were used for STN targeting. Quadripolar DBS electrodes (model 3387; Medtronic, Minneapolis, MN, USA) were implanted under local anesthesia, and motor function and adverse effects were strictly monitored by macro-stimulation. The implantable pulse generator (IPG) (Kinetra 7428; Medtronic) was implanted subclavicularly under general anesthesia. The precision of electrode placement was confirmed by postoperative MRI (Fig. 1).

2.3. DBS programming

IPG was regularly initiated 1 day after implantation. We adjusted the DBS parameters one month after implantation as the local edema disappeared and optimized the programming individually according to the results of the post-operative 1.5-T MRI, which can perfectly determine the spatial association between the contacts and the STN. The best contact and most favorable parameters were chosen based on the most satisfactory motor effects with the fewest adverse reactions.

2.4. Statistical analysis

All statistical analyses were performed using GraphPad prism 6.0 (GraphPad Software; San Diego, California, USA). Results are expressed as mean ± standard deviation (SD). Statistical analysis comprised analysis of variance and post-hoc analysis with the Student's t-test after assessing the normality of the data distribution. A p value of <0.05 was considered statistically significant.

3. Results

The mean age of all patients at the time of surgery was 29.8 ± 15.4 years (range, 17–68 years). The mean neuroleptic exposure was 12.7 ± 12.7 months (range, 6–48 months) and the mean follow-up time was 65.6 ± 30.4 months (range, 12–105 months), and four of the 10 patients received a battery replacement. The mean battery life was 5.5 years (range, 5–7 years). The clinical demographics of the patients are shown in Table 1.

3.1. Motor function

Nine of the 10 patients who had undergone the stereotactic operation benefitted remarkably from STN-DBS. Motor function, as reflected by the BFMDRS score, also improved. Compared with baseline scores, BFMDRS movement total scores were improved by 55.9± 28.3% ($p = 0.043$) at 1 week, 87.3± 17.0% ($p < 0.01$) at 6 months, and 88.3± 21.6% ($p = 0.025$) at the last follow-up visit (Table 2A and Fig. 1-C, 1-D). One patient turned the DBS off in his daily life for one year without any discomfort and, strikingly, he even could participate in light exercise (morning jogging) without any relapses. One patient showed a significant improvement in total BFMDRS score at the first two follow-ups, with scores improving by 73.3% and 85.8%, respectively, while he achieved a slight improvement (25%) in total BFMDRS score at the last follow-up.

Five patients demonstrated moderate amelioration on the first postoperative day, which is likely the result of the microlesion effect. The noticeable clinical efficacy manifested within one week in two patients, while one patient's total BFMDRS score decreased after 6 months. The immediately distinct relapses of the TD symptoms were observed with the DBS off, and immediately improved when the DBS was re-initiated at the second follow-up visit.

3.2. Extrapyramidal syndrome assessment

The AIMS scores showed a sharp reduction compared with that during the pre-surgical assessment (AIMS score, 18.0 ± 10.0). The analysis suggested that the AIMS score was reduced to 9.0 ± 7.5 ($p = 0.036$, improved by 53.3± 26.7%) at the first follow-up, to 2.7 ± 3.7 ($p < 0.01$, improved by 88.4± 16.1%) at the second follow-up, and to 2.1 ± 4.6 ($p < 0.01$, improved by 93.6± 12.4%) at the last follow-up visit (see Fig. 1-E).

3.3. Psychiatric evaluation

One patient refused to receive psychiatric assessment; all other

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