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Effect of bilateral subthalamic deep brain stimulation on diphasic dyskinesia

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Abstract

Objectives: The goal of this study was to assess the effect of bilateral subthalamic deep brain stimulation (STN DBS) on levodopa-induced diphasic dyskinesia in patients with Parkinson disease (PD).
Patients and methods: Six PD patients with diphasic dyskinesia were included in this study. Prior to surgery, the duration and severity of dyskinesia were determined in each patient, along with the Unified Parkinson Disease Rating Scale score and Hoehn and Yahr stage. Bilateral STN electrode implantation was performed during a single operation.
Results: The median duration of the follow-up period was 21.5 months (range 14–24 months). STN DBS had a beneficial effect on diphasic dyskinesia in all patients. At the last follow-up, 3 patients had no dyskinesia and 1 had only a small amount of peak-dose dyskinesia. One patient showed a reduction in the duration of diphasic dyskinesia, despite a lack of reduction in the total duration of dyskinesia. In the last patient, although the total duration of dyskinesia increased, the pattern of dyskinesia changed from severe painful disabling dyskinesia to the less severe peak-dose type of dyskinesia. There were no intraoperative or postoperative surgical complications.
Conclusions: Bilateral STN DBS is good at reducing diphasic dyskinesia, and it can be a good therapeutic option for patients with diphasic dyskinesia.

Keywords: Deep brain stimulation (DBS); Diphasic dyskinesia; Parkinson disease; Subthalamic nucleus (STN); Motor complications

1. Introduction

Diphasic dyskinesia is defined as an abnormal involuntary movement that appears at the beginning and at the end of the levodopa effect, but not during the peak of the levodopa effect in patients with Parkinson disease (PD). The rising and falling of plasma levels of levodopa is thought to be responsible for this phenomenon. The movements associated with diphasic dyskinesia can be dystonic, choreic, or a mixture of the two types [1]. These movements are typically stereotyped and repetitive, and they may be accompanied by a worsening of akinesia [2]. In many patients, diphasic dyskinesia is more prominent in the lower extremities than in the upper extremities, and it tends to be more severe at the end of the dose than at the beginning of dose. Diphasic dyskinesia is occasionally accompanied by severe pain and autonomic changes [3]. It usually affects patients with early-onset disease [3–5] and tends to diminish the patient's quality of life [6]. In the literature, the prevalence of diphasic dyskinesia in patients with PD reaches up to 20% [7]. The treatment of diphasic dyskinesia is difficult, and more frequent or higher doses of levodopa, dopamine agonists, liquid levodopa/carbidopa, or subcutaneous apomorphine can be tried but are usu-

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ally ineffective. Surgery can be considered in these cases [8].

Subthalamic deep brain stimulation (STN DBS) is an established treatment for the motor complications in patients with PD. Although most reports on the effects of STN DBS in levodopa-induced dyskinesia (LID) were focused on the treatment of peak-dose dyskinesia, several studies included the improvement of diphasic dyskinesia by STN DBS [9–13]. The objective of this study was to evaluate the effect of bilateral STN DBS on diphasic dyskinesia.

2. Materials and methods

2.1. Patients and clinical evaluation

The patients were recruited from the Movement Disorder Center (MDC) at Seoul National University Hospital. The inclusion criteria for STN DBS were clinically diagnosed idiopathic PD, levodopa responsiveness, severe motor complications (motor fluctuations or disabling LID, or both), no severe dementia, and normal brain MRI. All patients were admitted to the MDC, where 24-h-a-day continuous video monitoring and recording is available, and were evaluated by specialists in movement disorders. The patients continued their daily antiparkinsonian medication for 2 or 3 days after admission and were monitored for motor fluctuations and dyskinesias. Diphasic dyskinesia was defined as an abnormal involuntary movement appearing at the beginning and end of the levodopa effect, and the presence of diphasic dyskinesia in individual patients was confirmed by direct observation or by reviewing the recorded video segments. Before and during admission, the patients were repeatedly educated on how to differentiate between peak-dose dyskinesia and diphasic dyskinesia, using video recordings of their own movements when necessary. The Unified Parkinson Disease Rating Scale (UPDRS) score and Hoehn and Yahr (HY) stage were determined in both the *on* medication and *off* medication states. To increase the sensitivity, half-point was allowed for the UPDRS III. The severity (UPDRS item 33) and pattern of diphasic dyskinesia were documented. The *off* state was defined as the motor condition at 8–9 a.m. after at least 12 h of overnight withdrawal from antiparkinsonian medication, and the *on* state was defined as the maximum improvement following the usual first morning medication. In addition to video monitoring and recording, the patients were asked to complete a PD diary during admission. Every 30 min, the patient's motor status was recorded in the diaries as either *off*, *on* without dyskinesia or *on* with dyskinesia. The duration of dyskinesia and waking hours per day were assessed by reviewing the patients' PD diaries during admission. Additional information on the duration of the disease and the dosage of levodopa and other antiparkinsonian drugs were obtained. The levodopa equivalent daily dose (LEDD) was calculated as follows: 100 mg of standard levodopa = 133 mg of controlled-release levodopa = 10 mg bromocriptine = 1 mg pergolide = 1 mg pramipexole = 5 mg ropinirole [14,15]. Postoperative evaluation was carried out at 3, 6, and 12 months after surgery and annually thereafter. Six-month and annual follow-up evaluations were carried out as inpatient procedures in the MDC, with video recordings and diaries. In addition to the scheduled follow-up exams, the patients were also evaluated when the stimulator was reprogrammed.

2.2. Surgical procedure

The STN was located via stereotactic target planning with MRI using SurgiPlan^{TM} software and electrophysiological monitoring (microrecording and electrical stimulation) under local anesthesia. After the precise localization of the target point, the electrode for chronic stimulation (Medtronic 3389, Minneapolis, USA) was inserted. The electrode was then connected to an implantable pulse generator (IPG) implanted in the subclavicular area under general anesthesia. The patients underwent a single-stage operation in which both electrode insertion and IPG implantation were performed on the same day.

To verify the exact location of the electrodes, brain CT was performed 6 months after surgery, and the images were fused with the preoperative MR images for anatomical location.

3. Results

Six of the 58 PD patients who underwent STN DBS between May 2005 and February 2006 had diphasic dyskinesia. The characteristics of the six patients are shown in Table 1. The median values for age at the time of surgery, age at onset, and disease duration were 53, 42.5, and 9 years, respectively. Patient 2 had a previous history of right and left thalamotomy, 12 and 11 years earlier, respectively. These lesions were visible on the preoperative MRI, and they did not affect the surgical procedures. Patient 4 had a preexisting cardiac pacemaker, which had been implanted 10 years earlier. The duration of dyskinesia and severity of diphasic dyskinesia at baseline are summarized in Table 2. All patients had both beginning-of-dose dyskinesia and end-of-dose dyskinesia. The diphasic dyskinesias were of the choreodystonic type in all patients, with the exception of one (Patient 6) who showed increased tremor, rigidity, and akinesia. In 5 patients (Patients 1, 2, 4, 5, and 6), diphasic dyskinesia was painful. The duration of the beginning-of-dose dyskinesia or end-of-dose dyskinesia did not exceed 1 h in all patients. In addition to diphasic dyskinesia, Patients 2, 3, 4, and 5 had peak-dose dyskinesia, which caused no or minimal impairment in voluntary activity. In these patients, the two types of dyskinesia overlapped in time considerably. The patients were placed under 24-h video monitoring, and the video segments were used to educate the patient on how to differentiate between the two types of dyskinesias during the preoperative evaluation and postoperative follow-up.