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Case Report

Feasibility of Transcranial Direct Current Stimulation in Patients with Deep Brain Stimulation: a Case Report

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HIGHLIGHTS

- tDCS might be a potential add-on therapy in Parkinson's disease patients with DBS.
- Further study will be needed to clarify the effects of tDCS in PD with DBS.

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Feasibility of Transcranial Direct Current Stimulation in Patients with Deep Brain Stimulation: a Case Report

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ABSTRACT

Although deep brain stimulation (DBS) has been reported to be effective to ameliorate motor and non-motor dysfunctions, freezing of gait (FoG) is often resistant to DBS in patients with Parkinson's disease (PD). Transcranial direct current stimulation (tDCS) has been reported as an alternative therapeutic strategy to ameliorate FoG in PD patients. In this case report, we describe the effects of cumulative tDCS over the primary motor cortex of the lower leg to reduce FoG in 2 cases of PD patients with DBS. Two PD patients who had undergone DBS of the subthalamic nucleus visited the rehabilitation medicine department for refractory FoG. Each patient received cumulative tDCS over the primary motor cortex of the lower leg over to reduce FoG. Neither patient required change in dose of dopaminergic medication during the tDCS period nor a significant side effect during and after tDCS. Although the FoG-questionnaire (FoG-Q) in case 1 showed no change after 10 tDCS treatments, the patient in case 2 reported a significant improvement of FoG-Q from 11 to 3 after 5 days of tDCS. We present the safety and feasibility of tDCS in PD patients with DBS who showed refractory FoG.

Keywords: Parkinson disease; Transcranial direct current stimulation; Deep brain stimulation; Freezing of gait

INTRODUCTION

The prevalence of Parkinson's disease (PD) is increasing more rapidly than other neurological disorders because of the aging population, longer life expectancy, and increased environmental exposures associated with industrialization [1]. The symptoms associated with PD progress gradually result in disability in the performance of daily activities despite optimal therapy [2]. Pharmacologic therapies based on dopamine are the primary treatment strategy for patients with PD motor symptoms, and deep brain stimulation (DBS) techniques have been established as an alternative to treat PD [3]. Especially, DBS can be useful for patients with PD who have complications such as off

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Conflict of Interest

The authors have no potential conflicts of interest to disclose.

periods or dyskinesias that are not responsive to medication adjustments [4]. Although DBS has been reported to be effective to ameliorate motor and non-motor dysfunctions, freezing of gait (FoG) is often resistant to DBS [5,6].

Non-invasive brain stimulation (NIBS), such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation (tDCS), are currently being explored as safer alternatives to modulate cortical excitability [7]. For adjunctive treatment, NIBS showed potential efficacy to improve motor dysfunctions for patients with PD [7]. Moreover, tDCS has been reported as an alternative therapeutic strategy to ameliorate FoG in PD patients [8]. Although NIBS such as tDCS could be a potential add-on therapy in PD patients with DBS, there is no consensus on tDCS in PD patients with DBS.

In this case report, we describe the effects of cumulative tDCS over the primary motor cortex of the lower leg (M1-LL) to reduce FoG in 2 cases of PD patients with DBS. We aimed to explore the feasibility of add-on tDCS in PD patients with FoG already undergoing DBS for motor dysfunctions.

CASE REPORT

A 74-year-old PD patient with Hoehn & Yahr stage V (case 1) who had undertaken DBS of the subthalamic nucleus (STN-DBS) 2 years prior visited the outpatient clinic of the rehabilitation medicine department for further management of refractory FoG. He developed rigidity and bradykinesia with resting tremor in left upper and lower extremities 13 years ago, and his symptoms had progressed slowly. There was no significant abnormality in brain magnetic resonance imaging (MRI) of case 1. His symptoms had been well controlled with dopaminergic medication for about 10 years. He was diagnosed as PD based with these clinical findings. A 68-year-old PD patient with Hoehn & Yahr stage IV (case 2) who had undergone STN-DBS 4 years prior was admitted to the rehabilitation medicine department for refractory FoG. He developed parkinsonism in left upper and lower extremities 11 years ago, and showed a slow progression of symptoms. There was no significant abnormality in his brain MRI. He had been treated with dopaminergic medication, showing good response but appeared levodopa-induced dyskinesia for 7 years. He was diagnosed as PD based with these clinical findings.

tDCS was applied using the DC-STIMULATOR MR (NeuroConn GmbH, Ilmenau, Germany). All interventions and assessments took place in the "on" state at the same time of the day for each patient. The electrodes were attached to a 5 cm × 5 cm-sized, water-soaked sponge placed on the scalp. The anodal electrode was placed over M1-LL corresponding to 1 cm posterior to Cz as determined by the international 10/20 electroencephalogram system, and the cathodal electrode was placed over the right deltoid as the extracephalic area. A constant current of 2 mA was administered for 20 minutes (current density: 0.80 A/m^2) [9]. Immediately after tDCS, each patient received comprehensive physical therapy including balance and gait training for 30 minutes by a physical therapist who did not participate in any functional evaluations. Fig. 1 shows the schematics of tDCS and images from case 1. The patient in case 1 underwent tDCS 10 times over a period of 4 weeks, once every 2 or 3 days. On the other hand, the patient in case 2 received daily tDCS for 5 consecutive days. There was no change in dose of dopaminergic medication during the tDCS period.

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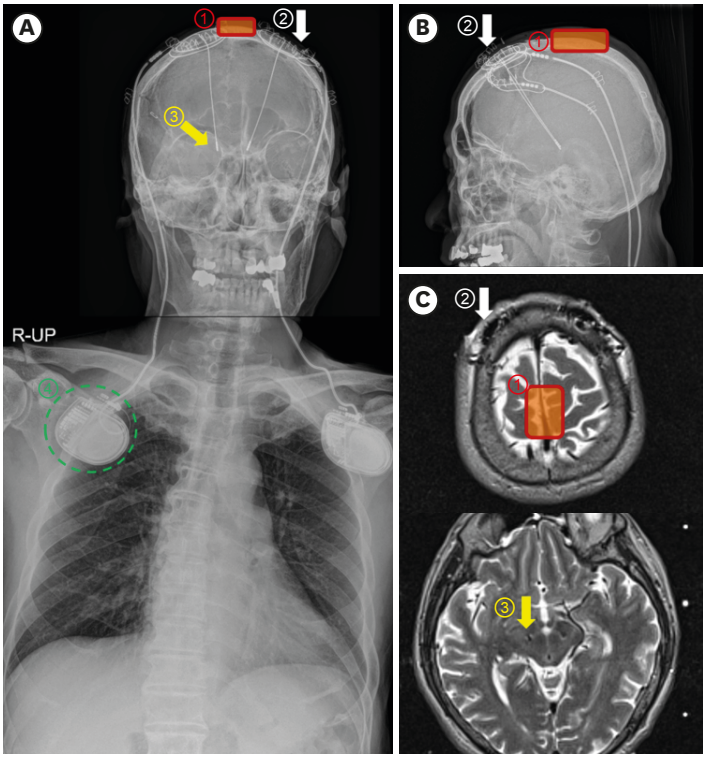

Fig. 1. Illustration of tDCS and imaging from the patient in case 1. (A) X-ray A-P view; (B) X-ray lateral view; (C) T2 brain magnetic resonance imaging transverse view. ① Anodal tDCS electrode; ② Stimulator of DBS; ③ Electrode of DBS; ④ Pulse generator of DBS.
tDCS, transcranial direct current stimulation; DBS, deep brain stimulation.

Table 1. Effects of tDCS

Cases	Variables	Before tDCS	After tDCS
Case 1	FoG-Q	15	15
	TUG	Unmeasurable due to severe FoG	
Case 2	FoG-Q	11	3
	TUG (sec)	18.4	15.2

tDCS, transcranial direct current stimulation; FoG-Q, freezing of gait-questionnaire; TUG, Timed Up and Go.

To evaluate each patient's FoG episodes, we used the FoG-questionnaire (FoG-Q) [10] before and after the tDCS sessions. In addition, the Timed Up and Go (TUG) test [11] was performed in case 2 for assessment of locomotor disturbances before and after the tDCS sessions.

In each patient, there was no significant side effect during or after each tDCS session. No changes in DBS parameters were made during or after tDCS. Although the FoG-Q in case 1 showed no change after 10 tDCS treatments, the patient in case 2 reported a significant improvement of FoG-Q after 5 consecutive days of tDCS. In addition, the TUG test in case 2 improved from 18.4 seconds to 15.2 seconds after 5 consecutive days of tDCS (Table 1).

DISCUSSION

In advanced PD, motor symptoms and non-motor symptoms that are refractory to conventional therapy pose therapeutic challenges. The success of DBS and advances in the

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understanding of the pathophysiology of PD have raised interest in NIBS as an alternative therapeutic tool [8]. A recent meta-analysis demonstrated that NIBS was effective on FoG in parkinsonism, and the effects were more prominent in PD than atypical parkinsonism [12]. Although the pathophysiology of FoG is not fully understood, recent theoretical frameworks have suggested that dysfunctional cortical and cerebellar projections to subcortical and brainstem locomotor regions may be involved in manifestation of FoG in PD [12]. The premotor and primary motor cortices may be targets for NIBS to modulate for improving gait ability and lower limb muscle activity in people with PD [13,14]. In addition, reduced activity in the supplementary motor area (SMA) contributes to the pathogenesis of start hesitation and FoG in PD [15]. The relatively large stimulation area of tDCS could produce modulating effects over SMA by tDCS over M1-LL. Based on these 2 hypotheses, M1-LL has been recommended as the main target of anodal tDCS to alleviate FoG in patients with PD.

In the 2 cases of the present study, the stimulator for DBS was in a position between M1-LL and the supraorbital area that is a common site for the cathodal electrode of tDCS [9]. To reduce the effect of electrical current by tDCS on the stimulator of DBS, the cathodal electrode was located on the extracephalic area. A report with the 3D field simulations based on the 3D finite showed that the maximum current density in the brainstem generated by the extracephalic reference electrodes was less than the current density generated by the cephalic reference electrodes, and the elicited cortical electric field distributions were not significantly different by variations in the reference electrode [16]. Therefore, tDCS with an extracephalic reference electrode would be similarly safe and effective as tDCS with a cephalic reference electrode. In the 2 cases of the present study, there was no significant adverse effect after tDCS. These results might suggest the safety of tDCS with an extracephalic reference electrode in patients with DBS. Although transcranial magnetic stimulation should be avoided in patients with intracranial metallic implants because of the risk of electromagnetically-induced undesirable currents, tDCS could be safe as long as the stimulation electrodes are kept away from the DBS leads.

The effect of tDCS on FoG was different between the 2 cases. Only case 2 showed a decrease of FoG after cumulative tDCS, although the number of tDCS sessions was higher in case 1 than case 2. The reason for this discrepancy might be the frequency of cumulative tDCS. Alonzo et al [17] reported that the change of motor cortical excitability was more prominent when tDCS was administered daily rather than every other day in healthy volunteers. Case 2 was administered daily tDCS for 5 days; however, case 1 received tDCS 2 or 3 times a week for 4 weeks. Therefore, daily tDCS could be recommended for clinical effects.

The present case report demonstrated the safety of tDCS in PD patients with DBS, producing no behavioral side effects and no change of DBS parameters after tDCS. Chhatbar et al. [18] reported that scalp tDCS produces a dose-dependent electrical field deep inside the brain despite a relative small current by 2 mA tDCS. In the present report, we could not exclude the effect of physical therapy on alleviation of FoG in each PD patient because there was no sham tDCS session in each case. Therefore, further study with a large number of participants will be needed to clarify the safety and effect of tDCS in patients with DBS. Despite these limitations, this study showed the feasibility of tDCS in PD patients with STN-DBS who showed refractory FoG.

Furthermore, this case report demonstrated that NIBS, such as tDCS, might be a potential add-on therapy in PD patients with DBS. However, further study will be needed to clarify the effects of tDCS in PD patients undergoing DBS.

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