

Dramatic Recovery of Freezing of Gait with Subthalamic Nucleus Deep Brain Stimulation

Letter to Editor,

Freezing of gait (FOG) is an episodic, abnormal gait pattern that accompany frequently in advanced Parkinson's disease (PD). FOG can markedly impair the quality of life in patients with PD, and the response to medical therapy is rather limited.^[1] The subthalamic nucleus deep brain stimulation (STN-DBS) is a well-established therapy in advanced PD for motor fluctuations and symptoms including akinesia, rigidity, and tremor.^[2,3] However, the efficacy of STN-DBS on axial symptoms such as FOG, postural instability, and gait impairment is rather insignificant and the literature data regarding its efficiency in FOG is particularly controversial.^[2-4]

A 73-year-old female patient with PD applied to our movement disorder polyclinic due to gait difficulty mainly characterized by FOG episodes that emerged during the last few months. The patient had been suffering from these episodes particularly during off periods and they were slight during "on" periods. Medical history interrogation revealed that the patient had PD for more than 20 years and the clinic had started initially with slowness on the right side and also involved the other side in the following years. Due to the uncontrolled motor symptoms including motor fluctuations, dyskinesias, prolonged off periods, and FOG episodes, the patient had undergone STN-DBS (The St. Jude Medical Infinity™ DBS System) surgery 7 years ago which had provided a marked improvement in these motor symptoms including FOG episodes. On admission to our center, the patient was receiving treatments of levodopa/carbidopa/entacapone (4 × 75 mg/18.75 mg/200 mg), rasagiline 1 × 1 mg, and ropinirole 1 × 2 mg. The neurological exam, at the off period (12 h after the levodopa dose), showed severe FOG episodes during initiation of gait, turnings, and walking through narrow spaces [Video 1]. There was also slowness of movements and a shortened stride length, however, the main problem and the newly onset symptomatology leading to functional decline was FOG episodes. Remarkably, an attempt of levodopa/carbidopa/entacapone 150 mg/37.5 mg/200 mg provided considerable improvement in FOG episodes during the "off" period. However, the improvement in the FOG episodes during the "on" period was minimal, albeit marked improvement in other Parkinsonian symptoms including bradykinesia, rigidity, and gait velocity were achieved. Of note, the evaluations during the stimulation-off and medication-off period revealed marked slowing of the movements and generalized rigidity after minutes closing the stimulation in addition to deterioration of FOG. During stimulation-off medication-on period, the patient still suffered from severe FOG episodes.

Due to these re-emerging FOG episodes, the patient had fallen several times over the last month both during medication "on"

and "off" periods. Besides, she had fear of falling intensely that also limited her mobilization markedly. The new freezing of gait questionnaire (NFOG-Q)^[5] score was 13 points. The initial stimulation parameters were as follows: amplitude 1.5 V (right), 1.7 V (left), pulse width 60 μs, frequency 130 Hz in monopolar mode bilaterally with left STN (C+;0-) and right STN (C+;8-). The stimulation amplitudes were gradually increased up to 2.5 A bilaterally which yielded a rapid and dramatic improvement in FOG episodes [Video 2]. The follow-up interview 2 weeks later, on the same medications with the pre-adjustment state, revealed that the FOG episodes occurred rarely within this period, and she could mobilize without aid and the fear of falling was nearly over. The NFOG-Q score, this time, was evaluated as 5 points.

DISCUSSION

STN-DBS is a critical method in the treatment of tremor, "on/off" fluctuations, and dyskinesia. Besides, many authors support that STN-DBS is effective against FOG in PD.^[2,3] However, in comparison to other motor symptoms, the benefit of DBS on FOG is still a controversial issue.^[2,3,6] For instance, if the beneficial effect of DBS on axial symptoms and FOG persists over the long term is still a complicated issue that remains to be clarified.^[3] In a large group of patients with long-term follow-up after STN-DBS (more than 2 years of period),^[3] evaluations during medication-off states showed that FOG was lower during the on-stimulation condition in comparison to the off-stimulation condition and also in comparison to that at baseline (pre-DBS), suggesting that STN-DBS has a long-term effect on FOG. On the other hand, the general concept is that the "on" medication FOG does not improve with STN-DBS which is explained by the underlying deficits of nondopaminergic neurotransmitters in "on" FOG, which is rather distinct from the other motor manifestations of PD.^[3,7] Furthermore, there are also rare reports mentioning newly emerging "on" FOG episodes after STN-DBS that strictly complicate the discussions.^[4,8] We also know that inadequate frequency or amplitude settings can cause DBS-induced or aggravated FOG. Particularly, high frequency combined with higher amplitude is more likely to aggravate FOG.^[2] The varying mechanisms underlying distinct forms of FOG and the individual differences may be responsible for these conflicting results regarding the response of FOG to STN-DBS therapy.^[3] For instance, the involvement of the disturbance in the cholinergic system and noradrenergic network have also been demonstrated in the pathophysiology of some subgroups of FOG, particularly the "on" FOG episodes which do not respond to dopaminergic treatments.^[9,10] The efficiencies of amantadine, acetylcholine esterase inhibitors, and methylphenidate are studied in

small-scale studies, however, they yielded only modest benefits.^[1] The STN stimulation does not directly lead to striatal dopamine release, however, it may activate the dopamine motor system by inhibiting over-activated STN neurons, thus improving FOG during the off-medication state.^[6] Of note, there is strong evidence that STN-DBS generates excitatory and inhibitory postsynaptic potentials in STN neurons through alterations of both glutamatergic and gamma-aminobutyric acidergic (GABAergic) afferents.^[11] Possibly, the recovery of the increased glutamatergic activity in the STN by DBS may be responsible for the dramatic resolution of FOG episodes by DBS adjustments which could not be achieved by levodopa therapy. In accordance with this, the contribution of glutamatergic neurotransmission in the axial symptoms of PD and FOG has been mentioned in recent reports.^[12] However, to elucidate the underlying pathophysiology of the recovery of FOG by DBS stimulation in these particular patients, future prospective studies including a large number of patients are warranted. Intraoperative microelectrode recording studies using a virtual reality gait paradigm to elicit freezing behavior intraoperatively in those patients undergoing STN-DBS surgery may provide critical perspectives regarding the unknown aspects of FOG pathophysiology and the *mechanisms* of action underlying the efficacy of *DBS*.

In this report, we illustrate the dramatic benefit of STN-DBS therapy on FOG symptoms in a PD patient with prominent symptoms of FOG. The presentation of these specific cases may provide substantial perspectives to be kept in mind in clinical practice. The efficiency of DBS therapy in FOG, a problem of a transient network malfunction, even in the chronic phase of the therapy, may provide crucial contributions to the unknown aspects of DBS therapy, and also the pathophysiology of FOG.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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REFERENCES

- Zhang LL, Canning SD, Wang XP. Freezing of gait in parkinsonism and its potential drug treatment. *Curr Neuropharmacol* 2016;14:302-6.
- Moreau C, Defebvre L, Destee A, Bleuse S, Clement F, Blatt JL, *et al.* STN-DBS frequency effects on freezing of gait in advanced Parkinson disease. *Neurology* 2008;71:80-4.
- Kim R, Kim HJ, Shin C, Park H, Kim A, Paek SH, *et al.* Long-term effect of subthalamic nucleus deep brain stimulation on freezing of gait in Parkinson's disease. *J Neurosurg* 2019;131:1797-804.
- Mei S, Li J, Middlebrooks EH, Almeida L, Hu W, Zhang Y, *et al.* New onset on-medication freezing of gait after STN-DBS in Parkinson's disease. *Front Neurol* 2019;10:659.
- Hulzinga F, Nieuwboer A, Dijkstra BW, Mancini M, Strouwen C, Bloem BR, *et al.* The new freezing of gait questionnaire: Unsuitable as an outcome in clinical trials? *Mov Disord Clin Pract* 2020;7:199-205.
- Kim R, Kim HJ, Kim A, Kim Y, Kim AR, Shin CW, *et al.* Depression may negatively affect the change in freezing of gait following subthalamic nucleus stimulation in Parkinson's disease. *Parkinsonism Relat Disord* 2017;44:133-6.
- Nonnekes J, Snijders AH, Nutt JG, Deuschl G, Giladi N, Bloem BR. Freezing of gait: A practical approach to management. *Lancet Neurol* 2015;14:768-78.
- Davis JT, Lyons KE, Pahwa R. Freezing of gait after bilateral subthalamic nucleus stimulation for Parkinson's disease. *Clin Neurol Neurosurg* 2006;108:461-4.
- Ono SA, Sato T, Muramatsu S. Freezing of gait in parkinson's disease is associated with reduced 6-[(18) F] Fluoro-l-m-tyrosine uptake in the locus coeruleus. *Parkinsons Dis* 2016;2016:5430920.
- Bohnen NI, Kanel P, Zhou Z, Koeppel RA, Frey KA, Dauer WT, *et al.* Cholinergic system changes of falls and freezing of gait in Parkinson's disease. *Ann Neurol* 2019;85:538-49.
- Lee KH, Chang SY, Roberts DW, Kim U. Neurotransmitter release from high-frequency stimulation of the subthalamic nucleus. *J Neurosurg* 2004;101:511-7.
- O'Gorman Tuura RL, Baumann CR, Baumann-Vogel H. Beyond dopamine: GABA, glutamate, and the axial symptoms of Parkinson disease. *Front Neurol* 2018;9:806.

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