

# Deep Brain Stimulation of the Internal Segment of the Globus Pallidus in Delayed Runaway Dyskinesia

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**Background:** Dyskinesias that occur during a period without medication after embryonic cell transplantation have been commonly reported in double-blind trials; however, to date, they have not been reported in the few patients who participated in open-label pilot studies.

**Design:** Single case observation with preoperative and postoperative data, and intraoperative single-cell physiology.

**Patient:** A patient who underwent embryonic cell transplantation in 1993 as part of the University of South Florida open-label study was referred for evaluation of intractable dyskinesia of the right arm. The dyskinesia was present during evaluation of the patient after a 12-hour period without medication and was clinically dis-

abling. It was manifested as a severe groping movement of the hand. Intraoperative physiologic evaluation revealed decreased firing rates in the internal segment of the globus pallidus.

**Results:** Deep brain stimulation of the internal segment of the globus pallidus resulted in resolution of the dyskinesia.

**Conclusion:** This case highlights the delayed development of runaway dyskinesia after a period without medication as an important potential long-term adverse effect of embryonic cell transplantation in patients with Parkinson disease.

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**R**UNAWAY DYSKINESIA HAS been reported as a complication of embryonic striatal transplantation of dopaminergic cells in medication-refractory Parkinson disease (PD).<sup>1-4</sup> The mechanism of runaway dyskinesia remains unknown, although it has been speculated that factors that may influence its development may include partial graft survival; graft growth, graft location, and the number of grafts; graft cell types; and method used in performing graft transplantation.<sup>1-4</sup> Although the few patients in the open-label pilot study did not exhibit runaway dyskinesia at the initial follow-up, we report the case of a patient with delayed dyskinesia that developed after a period without medication (also known as “off medication”) who responded favorably to deep brain stimulation (DBS).

## METHODS

This is a single case report of a patient followed up 10 years after embryonic cell trans-

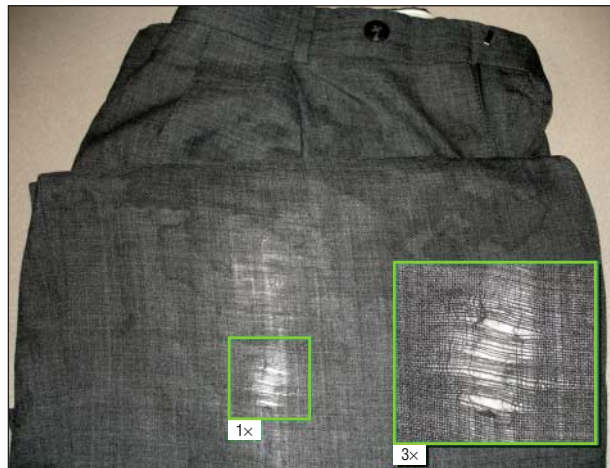
plantation was performed to treat PD. Before surgery, the patient's condition was evaluated off medications and when he was receiving medication (also known as “on medications”). After surgery, he was evaluated during periods with medication—with stimulation, without medication—with stimulation, with medication—without stimulation, and without medication—without stimulation.

## REPORT OF A CASE

A 50-year-old man with a 15-year history of PD received bilateral embryonic transplants into the postcommissural putamen region (patient 4 in the University of South Florida transplantation pilot study<sup>5</sup>). He reported that his symptoms improved for 1 to 2 years after the transplantation, but then progressively worsened. Approximately 11 years after the transplantation procedure, the patient was seen for surgical evaluation because of intractable dyskinesia of the right arm. In addition to the severe right-sided dyskinesia, he had tremor, asymmetric rigidity, festinating

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**Figure 1.** Typical hole in the pants leg caused by groping hand movement in a patient with runaway off-medication dyskinesia. A white background was used behind the hole for contrast. This photograph has the main hole at 1 and 3 times magnification.

gait, frequent falling, and postural instability. The dyskinesia, which had developed during the preceding 3 years, was characterized by a groping movement of the right hand and was worse with medication. The friction from the movement resulted in large holes in the patient's right upper pants leg (**Figure 1**). The movement worsened progressively.

The dyskinesia was present when the patient's condition was evaluated during a 12-hour period without medication. "On-off medication" Unified Parkinson's Disease Rating Scale (UPDRS) testing demonstrated a significant levodopa response (42%; UPDRS score, 59 without medication and 34 with medication). Deep brain stimulation of the internal segment of the left globus pallidus (GPi) resulted in resolution of the dyskinesia and improvement in motor symptoms. Five GPi neurons measured during DBS surgery while the patient was without medication and dyskinetic had a mean firing rate (spikes per second) of 73.4. **Table 1** lists the cells recorded during surgery, and **Figure 2** shows a microelectrode recording obtained during surgery. The patient has been followed up for 6 months since DBS, with major clinical evaluations at baseline and at 142 and 198 days after surgery. At 142 days after surgery, the patient showed an improvement in UPDRS testing from baseline (49% improvement, UPDRS score of 30 without medication—with DBS; and 54% improvement, UPDRS score of 27 with medication—with DBS). At 198 days, the UPDRS score without medication—without DBS (for 12 hours) was 44, and with medication—without DBS was 33, which was a 44% improvement from baseline (**Table 2**).

#### COMMENT

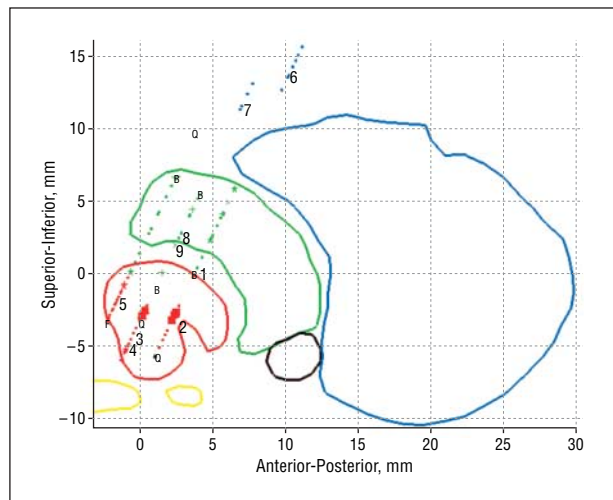
Embryonic nigral transplantation in our patient resulted in delayed runaway dyskinesia. The runaway dyskinesia developed approximately 11 years after the transplantation procedure, when the patient was not receiving any medication, and was effectively treated

**Table 1. Intraoperative Firing Statistics for Cells Encountered in the Surgical Procedure**

Neuron No.*	Firing Rate, Spikes/s	Mean $\pm$ SD ISI, ms
1 (GPi)	19	54 $\pm$ 32
2 (GPi)	90	11 $\pm$ 7
3 (GPi)	83	12 $\pm$ 10
4 (GPi)	130	8 $\pm$ 8
5 (GPi)	45	22 $\pm$ 19
6 (Striatum)	21	49 $\pm$ 25
7 (Striatum)	15	69 $\pm$ 57
8 (GPe)	74	14 $\pm$ 12
9 (GPe)	46	22 $\pm$ 32

Abbreviations: GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; ISI, interspike interval.

\*Neuron number corresponds to the location where the recording was obtained (represented in **Figure 2**). Single cells were sorted off-line using the Spike 2 software package (Cambridge Electronic Design, Cambridge, England).



**Figure 2.** Cells from the intra-operative microelectrode recording cells are labeled according to their occurrence in **Table 1**. Blue indicates striatum; green, external segment of the globus pallidus; red, internal segment of the globus pallidus; yellow, optic tract; and black, anterior commissure. Five microelectrode recording (MER) passes were performed; a sample of 3 of the passes is shown on an approximate 21.5-mm sagittal atlas plane. The squares in the internal segment of the globus pallidum indicate the presence of sensorimotor cells. On the x-axis, the positive numbers indicate the anterior direction; on the y-axis, the superior direction. B indicates locations in which border cells were identified during MER; F, locations in which fiber cells were identified during MER; and Q, locations that were found to be quiet during MER.

with GPi DBS. This long delay to development of off-medication dyskinesia is in some contrast to the findings in the double-blind studies in which runaway dyskinesia occurred 6 to 24 months after transplantation.<sup>1,2</sup> The findings in this case underscore the need for longer follow-up studies in research subjects with PD with grafts placed in the putamen. This case also illustrates that runaway dyskinesia may effectively be treated with GPi DBS, although the best approach will require further study.

Selected patients with PD have received fetal nigral implants since about 1987. These trials have demonstrated that transplanted cells can survive and even

grow in the human brain.<sup>4</sup> The promising results of small open-label studies spurred 2 prospective double-blind surgical trials.<sup>1,2</sup> The results of these trials, however, did not reproduce the success observed in open-label studies. Both the Denver-Columbia group and the Mount Sinai-University of South Florida group reported off-medication dyskinesia, later referred to as runaway dyskinesia. This adverse effect was observed in 15% of patients in the Denver-Columbia trial<sup>1</sup> and 56% of patients in the Mount Sinai-University of South Florida trial.<sup>2</sup>

While many groups have suggested possible mechanisms for runaway dyskinesia, the exact cause or causes remain unknown. Typically, dyskinesia is a complication of levodopa therapy<sup>6,7</sup> but has also been seen with DBS.<sup>8,9</sup> This hyperkinetic adverse effect has been hypothesized to result from pulsatile stimulation of dopamine receptors. This pulsatile stimulation may result in changes, mainly in firing pattern, of the basal ganglia structures.<sup>6</sup> Although the mechanism for this new phenomenon, runaway dyskinesia, is unknown, several groups have proposed theories that may lead to its genesis. Freed et al<sup>1</sup> have hypothesized that continued growth of the transplant may lead to an overflow of dopamine, resulting in dyskinesia even in the off-medication state. The delay in onset may at least be partially explained by this hypothesis. Olanow et al<sup>2</sup> have proposed a different explanation. They hypothesize that off-medication dyskinesia in transplant recipients may mimic diphasic dyskinesia, seen at the beginning and end of levodopa dose administration. In diphasic dyskinesia, low striatal dopamine concentrations are thought to be responsible for dyskinesia. Our patient demonstrated his worst UPDRS score (59) when dyskinetic and in the off-medication state. Typically, dyskinesia is associated with the best motor scores while taking medication. It could be argued that this patient had what would be diphasic dyskinesia, in which prominent dyskinesia was present but the patient was not completely in the on-medication state. Olanow et al<sup>2</sup> further suggest that immune rejection and partial reinnervation of the graft could also contribute to the imbalance leading to runaway dyskinesia.

The mean firing rate of the 5 GPi neurons reported in this paper reflect a normal GPi frequency of firing in PD. Papa et al<sup>10</sup> demonstrated that GPi firing rates decrease when a primate enters the on-medication state and again decrease when dyskinesia develops. In our patient, the normal GPi firing rates suggest a separate mechanism from levodopa-induced dyskinesia, as studied by Papa et al, perhaps some sort of innervation from the graft itself. The firing rates of the neurons and striatum of the external segment of the globus pallidum are also consistent with these data. To our knowledge, the GPi firing rate during diphasic dyskinesia has not been published, although, in theory, a decrease in rate may be expected. The groping motion in this patient could suggest involvement of the frontal striatal circuitry and possibly of the supplementary motor area and cingulate cortex,<sup>11,12</sup> and could also be a potential reason for the physiologic findings. This hypothesis cannot be substantiated by data provided from this single case. The findings in future subjects with off-medication dyskinesia should be studied, along with intraoperative physiology and functional imaging, in an effort to improve our understanding of potential mechanisms for such dyskinesia.

**Table 2. UPDRS Scores**

Time	Condition of Testing and UPDRS III (Motor) Scores*		Medication: Levodopa Equivalent, mg†
Baseline	Without medication, 59	With medication, 34	1200
142 Days	With medication— with DBS, 27	Without medication— with DBS, 30	1000
198 Days	Without medication— without DBS, 44	With medication— without DBS, 33	650.25

Abbreviations: DBS, deep brain stimulation; UPDRS, Unified Parkinson's Disease Rating Scale.

\*The patient improved with DBS, with resolution of dyskinesia in both the on-medication and off-medication states. The improvement in off-medication score at 198 days could represent either failure to wash out the effects of medication and DBS (12-hour washout was used), chronic effect of DBS, or micropallidotomy or lesion effect from the DBS electrode.

†Total levodopa equivalent dose = regular levodopa + (pramipexole × 67).

This article stresses the need for longer follow-up of patients receiving transplant therapy for the treatment of PD. Complications of surgical therapy for PD, such as those previously seen with gamma knife or radiation treatment<sup>13</sup> and those after graft-induced runaway dyskinesia, underscore the importance of monitoring for both delayed benefits and delayed complications of therapy. Although this is only one case report, much can be potentially learned from the manifestations and treatment of delayed runaway dyskinesia.

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