https://doi.org/10.14802/jmd.20090 / J Mov Disord 2021;14(3):239-241
pISSN 2005-940X / eISSN 2093-4939

LETTER TO THE EDITOR

Parkinson's Kinetigraph in the Selection of Levodopa-Carbidopa Intestinal Gel for Motor Fluctuations Refractory to Deep Brain Stimulation

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Despite rigorous selection and programming, some patients with Parkinson's disease (PD) may not respond optimally to deep brain stimulation (DBS). Some evidence supports the joint use of DBS and other therapies, such as levodopa-carbidopa intestinal gel (LCIG). There is increasing interest in the use of wearable technologies in selecting patients for advanced therapies. Here, we present a patient with ongoing poorly controlled symptoms following DBS for whom the selection and titration of adjunctive LCIG was facilitated by the use of wearable technology.

We report the case of a 47-year-old female who was diagnosed with early-onset PD at the age of 36. She had a previous episode of central nervous system demyelination but had remained relapse-free for several years. There was no family history of parkinsonism. She initially received levodopa with subsequent addition of entacapone and ropinirole and showed a good dopaminergic response, with early motor fluctuations. Ropinirole was discontinued due to impulse control disorder (ICD) manifesting as problem gambling, but despite taking levodopa 600 mg daily plus rasagiline, she continued to have marked off periods and developed dyskinesia at higher levodopa doses. Her gambling did not fully resolve with cessation of ropinirole. She was referred for consideration of DBS surgery seven years after symptom onset. Her levodopa challenge showed a good levodopa response, with a UPDRS-III OFF score of 73 and an ON score of 4. She was deemed to be a good candidate for bilateral subthalamic nucleus (STN) DBS.

DBS was successfully implanted with no postoperative complications. She showed an initial response to DBS, with a one-year Unified Parkinson's Disease Rating Scale part III (UPDRS-III) OFF score of 34 and an ON score of 6 as well as a reduction of her levodopa dose to 400 mg/day. Her gambling did improve on this lower levodopa dose. However, she complained of significant residual motor fluctuations, limb and cranial dystonia, and disabling off time. Parkinson's Kinetigraph™ (PKG, Global Kinetics Corporation, Melbourne, Australia) recording showed significant uncontrolled bradykinesia and off time (Figure 1A, C). She was therefore discussed at our advanced therapies multidisciplinary team. A review of her DBS leads showed no suggestion of lead malpositioning (Supplementary Figure 1 in the online-only Data Supplement), and she did not benefit from changes to her therapeutic contacts. At the time of assessment, she exhibited the following parameters: left 1- 2+, amplitude 4.2 V, pulse width 60 μs, frequency 130 Hz; right 10- 11+, amplitude 4 V, pulse width 60 μs, frequency 130 Hz. She declined to be considered for revision surgery. Apomorphine was felt to be an undesirable choice, given her ongoing difficulties with ICD.

A nasojejunal trial of LCIG was performed 10 years after symptom onset and showed significant improvement compared to DBS alone and an additional response in combination with

Received: August 11, 2020 **Revised:** September 23, 2020 **Accepted:** October 15, 2020
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JMD
J Mov Disord 2021;14(3):239-241

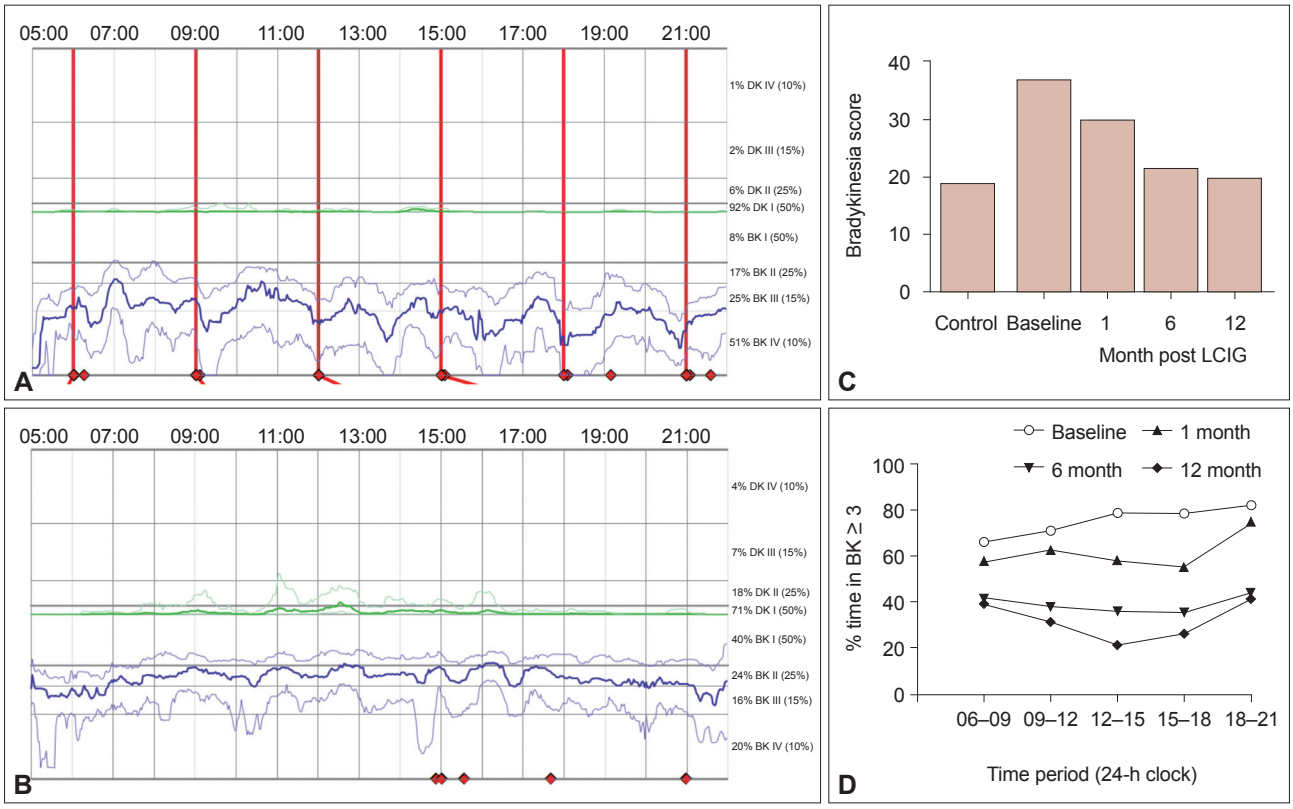

Figure 1. Median dyskinesia (green ± interquartile range) and bradykinesia (blue ± interquartile range) scores over time at baseline (A) and 12 months following the addition of LCIG therapy (B). Red lines indicate oral medication dosing and dark gray horizontal lines indicate optimal levels of bradykinesia and dyskinesia. Median bradykinesia scores compared to the median control value over 12 months of LCIG (C). Changes in the amount of time spent in the OFF state as defined by a bradykinesia score ≥ 3 during LCIG titration (D). DK: dyskinesia, BK: bradykinesia, LCIG: levodopa-carbidopa intestinal gel.

DBS. UPDRS-III scores in all four states were as follows: DBS OFF/LCIG OFF 68; DBS ON/LCIG OFF 39; DBS OFF/LCIG ON 14; DBS ON/LCIG ON 6.

She therefore underwent percutaneous endoscopic gastrojejunostomy insertion and commenced long-term LCIG therapy at 1.6 mL/h. PKG results indicated persistent bradykinesia and off-time at one month leading to a gradual titration up to 1.8 mL/h with demonstrable improvement in both metrics (Figure 1C, D). She reported an improvement in on-time and quality of life, as measured by the Parkinson's Disease Questionnaire-39 (PDQ-39) summary index, which improved from 48 at baseline to 35 after 12 months of therapy. Objective improvements in PKG monitoring were also observed, with on-time and bradykinesia levels improving significantly without excessive dyskinesia (Figure 1B-D). No further problems with gambling or other ICD were reported.

Despite the good evidence base for DBS in advanced PD, a suboptimal motor response is seen in a minority of cases. In such cases, revision of the lead position, programming and medical management may improve outcomes in many instances.[1] Our patient continued to have marked disabling "off" periods despite optimal lead placement and a satisfactory motor response at levodopa challenge, raising the potential need for additional medical therapies. The selection and optimization of such complex cases may be challenging and was facilitated by the use of wearable technology in the form of PKG.

Regidor et al.[2] reported 19 patients (mean disease duration 19.4 years) who underwent dual therapy with STN-DBS and LCIG, with significant improvements in overall and axial UPDRS-III scores. Kumar et al.[3] reported seven patients in whom LCIG was used as an adjunct to DBS, three of whom underwent bilateral STN procedures. Improvements in motor fluctuations as measured by UPDRS-IV were observed. An additional series of six patients (3 bilateral STN-DBS) showed improvements in UPDRS-IV scores and quality of life as measured by the PDQ-39.[4] Benefit occurred in those with both poor and optimal lead location, suggesting a possibility for LCIG to benefit increasing wearing off due to disease progression. In our case, disease progression may explain worsening fluctuations, but further increases in oral levodopa were not tolerated due to gambling. Recently, three DBS patients were reported in whom improvements in wearing-off occurred with the addition of

LCIG, although only two patients with bilateral STN-DBS continued long-term treatment.[5] Elkouzi et al.[4] proposed an algorithm for consideration of LCIG in those with persistent motor fluctuations post-DBS.

Appropriate patient selection is particularly important when selecting patients for adjunctive medical therapy when DBS has failed to provide sufficient benefits despite reasonable improvement in motor UPDRS scores. Questionnaires and patient diaries are validated to identify off-time but are reliant on accurate completion and training. Wearable devices to monitor symptoms represent a novel source of information for clinicians in assessing PD symptoms, providing quantitative measures of motor fluctuations over extended periods of time. The PKG is an accelerometer-based wearable device that produces scalar output measures of bradykinesia and dyskinesia that correlate with clinical measures.[6] In this case, routine use of the PKG identified significant off periods within the range of uncontrolled bradykinesia,[7] despite a relatively good response to DBS measured by the UPDRS-III. The subsequent use of PKG allowed optimization of off time and bradykinesia into a "controlled" range, allowing identification of a treatment target and titration of LCIG to achieve this. Recent reports suggest the utility of PKG to identify candidates for advanced therapies.[8] We suggest that it may aid decision-making in complex cases with suboptimal DBS response and help to verify the response to adjunctive LCIG treatment and guide titration in such cases.

Ethics Statement

The authors confirm that the approval of an institutional review board was not required for this work. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.20090.

Conflicts of Interest

Yassine Noui has no competing interests. Monty A. Silverdale has received grants from the Michael J. Fox Foundation, Parkinson's UK, NIHR; travel grants from Abbvie and Bial. Julian Evans has received travel grants from Medtronic. Lucy Partington-Smith has received travel grants from Medtronic. Christopher Kobylecki has received grants from Parkinson's UK and the Michael J Fox Foundation; speaker fees from Britannia and Bial Pharma; and support to attend international meetings from Abbvie.

Acknowledgments

None

Author Contributions

Conceptualization: Christopher Kobylecki. Data curation: all authors. Investigation: Christopher Kobylecki, Monty Adam Silverdale, Julian Evans, Lucy Partington-Smith. Methodology: Christopher Kobylecki. Project administration: Christopher Kobylecki, Yassine Noui. Supervision: Christopher Kobylecki. Writing—original draft: Christopher Kobylecki, Yassine Noui. Writing—review & editing: all authors.

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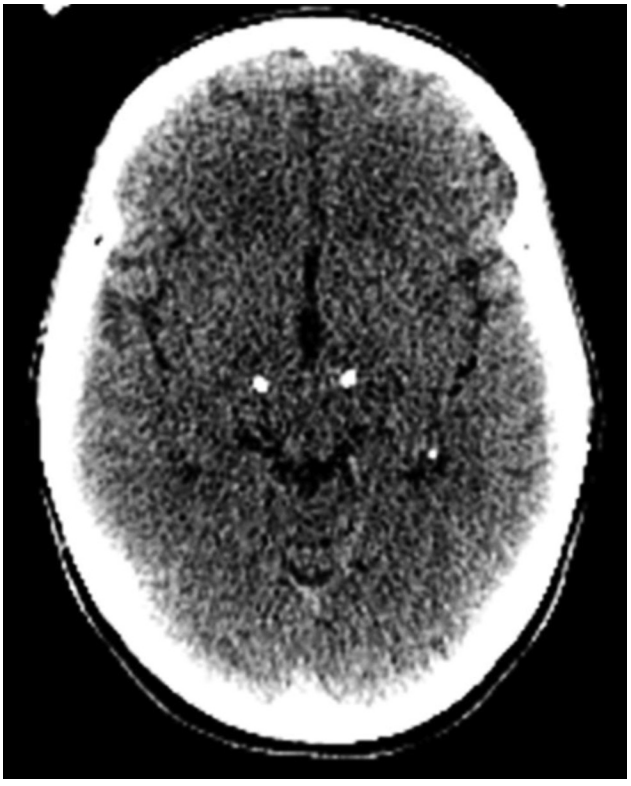
REFERENCES

1. Kluger BM, Foote KD, Jacobson CE, Okun MS. Lessons learned from a large single center cohort of patients referred for DBS management. Parkinsonism Relat Disord 2011;17:236-239.
2. Regidor I, Benita V, Del Álamo de Pedro M, Ley L, Martinez Castrillo JC. Duodenal levodopa infusion for long-term deep brain stimulation-refractory symptoms in advanced Parkinson disease. Clin Neuropharmacol 2017;40:103-107.
3. Kumar N, Murgai A, Naranian T, Jog M, Fasano A. Levodopa-carbidopa intestinal gel therapy after deep brain stimulation. Mov Disord 2018;33:334-335.
4. Elkouzi A, Ramirez-Zamora A, Zeilman P, Barabas M, Eisinger RS, Malaty IA, et al. Rescue levodopa-carbidopa intestinal gel (LCIG) therapy in Parkinson's disease patients with suboptimal response to deep brain stimulation. Ann Clin Transl Neurol 2019;6:1989-1995.
5. Bautista JMP, Oyama G, Nuermaimaiti M, Sekimoto S, Sasaki F, Hatano T, et al. Rescue levodopa/carbidopa intestinal gel for secondary deep brain stimulation failure. J Mov Disord 2020;13:57-61.
6. Griffiths RI, Kotschet K, Arfon S, Xu ZM, Johnson W, Drago J, et al. Automated assessment of bradykinesia and dyskinesia in Parkinson's disease. J Parkinsons Dis 2012;2:47-55.
7. Odin P, Chaudhuri KR, Volkmann J, Antonini A, Storch A, Dietrichs E, et al. Viewpoint and practical recommendations from a movement disorder specialist panel on objective measurement in the clinical management of Parkinson's disease. NPJ Parkinsons Dis 2018;4:14.
8. Khodakarami H, Farzanehfar P, Horne M. The use of data from the Parkinson's KinetiGraph to identify potential candidates for device assisted therapies. Sensors (Basel) 2019;19:2241.



Supplementary Figure 1. Postoperative axial CT brain in radiological orientation (right on left side of figure) showing deep brain stimulation electrodes.