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ORIGINAL COMMUNICATION

Optimizing the selection of Parkinson's disease patients for neuromodulation using the levodopa challenge test

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Abstract

Background In Parkinson's disease (PD), early stages are associated with a good long-duration response and as the disease advances, the short-duration response predominates. The transition between the long-duration and short-duration responses may be an important and measurable intermediate stage. A critical criterion in determining the candidature for neuromodulation is a beneficial response to an 'off–on' levodopa challenge test. This test is usually reserved for those that have already developed marked short-duration response and are candidates for deep brain stimulation (DBS) surgery. However, identifying those that are in transition may allow DBS to be offered earlier.

Objective The objective of the study was to determine if the transition from a long-duration to a short-duration response can be assessed on a levodopa challenge test.

Methods An 'off–on" levodopa challenge test was done in sixty-five PD patients divided into four groups based on the disease duration.

Results OFF motor scores increased in all groups [Mean ± STD; 22.94 ± 8.52, 31.53 ± 9.87, 34.05 ± 9.50, and 33.92 ± 10.15 in groups 1–4, respectively] while a significant response to medication was maintained on 'off–on' testing. The mean levodopa equivalency dose in groups 1 and 2 was significantly less than in groups 3 and 4. This transition occurred between years 7 and 9 of disease duration.

Conclusion Performing a regular levodopa challenge test, when levodopa dose increases substantially, should be considered to determine the ideal time for DBS in patients with Parkinson's disease.

Keywords Parkinson's disease · Levodopa challenge test · Deep brain stimulation · Short-duration response · Long-duration response

Introduction

The United States Food and Drug Administration (USFDA) approved levodopa for the treatment of motor symptoms of PD in 1970. Though many new drugs have since been introduced, none is as efficacious as levodopa [1]. Even in the advanced stages of PD, levodopa has a beneficial effect, though in higher doses. This is associated with significant complications in the form of motor fluctuations and dyskinesias [2]. The therapeutic response to levodopa consists of two components: Long-duration response (LDR) and Short-duration response (SDR) [3]. LDR is the more sustained response, occurs after chronic administration of levodopa, and is independent of the pharmacokinetics of the drug. It denotes a better state of neurotransmitter buffering than SDR, which parallels the plasma levodopa levels [3]. SDR is primarily responsible for the acute improvement in the motor symptoms after administration of levodopa and lasts for a few hours [3–5]. Unlike LDR, SDR can be measured by orally administering levodopa and assessing the motor benefits of stimulating the central dopamine receptors, the basis of the levodopa challenge test (LCT; 'off–on' test) [6].

The motor response to LCT is a critical screening tool for determining suitability for invasive interventions in PD-like neuromodulation with deep brain stimulation (DBS)

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or continuous intestinal infusion therapy with levodopa/carbidopa [7]. The best response in a patient to DBS is predicted by more than 30% improvement in the Movement Disorders Society Unified Parkinson Disease Rating Scale (MDS-UPDRS) part III motor score on LCT and below this cut-off, surgery is not recommended [8]. Usually, patients selected for DBS are the ones with advanced PD with motor fluctuations while those early in their disease are managed conservatively. However, the EARLYSTIM study showed that neuromodulation improved the quality of life and non-motor and motor scores in PD patients treated at an average 7.3 years of disease duration, rather early in the timeline [9]. It has been shown that in advanced state of dopaminergic neuron degeneration, the non-nigral circuits become 'dopaminergic' and the aberrant dysfunctional dopamine release is responsible for the fluctuations contrary to the systematic storage, release and buffering of dopamine from the intact nigral terminals [10–13]. Thus, phenotypically, PD patients can be divided into an early group, those responding to the drug with no motor fluctuations and in the 'honeymoon period' of the disease and the advanced PD patients with fluctuations and motor complications. The early group patients have a good LDR while in the latter, SDR takes over secondary to dopaminergic cell loss [3, 14]. We hypothesize that as the LDR wanes, a transition from a combined LDR and SDR response to a solely SDR occurs, reflecting a switch to non-nigral (neuronal and glial) dopamine metabolism. Those that are in this middle stage represent an intermediate group where the switch from LDR to SDR is happening at the neuronal level. These patients start to exhibit motor fluctuations with increasing levodopa dose required for symptom control. They are the potential candidates for early neuromodulation if they can be identified on clinical examination.

Based on this hypothesis, the present study was conducted to evaluate if such an intermediate group could be identified. The clinical profile in PD patients, divided into four groups depending on the disease duration, was studied to determine if clinically recognizable features or a "response switch" was identifiable, suggesting susceptibility to SDR on an LCT. This may be a method to better identify patients to be considered for early neuromodulation.

Methods

Study participants

Sixty-five prospective patients with PD were recruited from the Movement Disorders Centre, University Hospital, London, Ontario, Canada (REB #107,253). Participants were included based on the following criteria: (1) have been diagnosed with idiopathic PD for at least 2 or more years (This arbitrary period of 2 years was used as by this time most other parkinsonian syndromes like progressive supranuclear palsy (PSP) or multiple system atrophy (MSA) can be differentiated clinically from idiopathic PD [15]; (2) be 45–85 years of age; (3) have been on stable doses of anti-Parkinson medication, including any levodopa preparation; and (4) be able to give informed consent. Participants were excluded on the following criteria: (1) history of any surgical intervention for treating PD (i.e. deep brain stimulation, levodopa-carbidopa intestinal gel); (2) extreme physical disability that impairs mobility assessment; (3) history or current diagnosis of unstable psychiatric condition; (4) presence of dementia or any other condition that prevents the ability of the participant to provide fully informed consent. All included patients had Montreal cognitive assessment (MoCA) testing and were excluded when they scored less than 23/30. Participants were divided into separate groups based on duration of disease: 2–5 years (group 1), 6–9 years (group 2), 10–13 years (group 3) and > 14 years (group 4). The Hoehn and Yahr (H & Y) scale was not chosen to separate patients into four groups. Based on the study by Zhao et al., the patients were divided into four groups based on an approximate median time to transit from one stage to the next in the timeline of disease progression in PD [16]. All participants underwent a detailed neurological examination before the levodopa challenge test.

Levodopa challenge test

The levodopa challenge test was done according to the CAPSIT-PD protocol [7]. Participants were instructed to take their last dose of levodopa at 8:00 PM on the night before the study and arrive at 9:00 AM the following morning to allow for an appropriate washout of levodopa. Similarly, dopamine agonists were withheld 24 h prior to the clinic visit for the study. Current medications were recorded as the daily levodopa equivalency dose (LED) which uses commonly accepted conversion factors [17]. Next, the motor examination portion (Part III) of the MDS-UPDRS was performed to provide a clinically defined OFF motor score. Participants were then instructed to take 120% of their regular levodopa dosage through 100/25 mg levodopa/carbidopa tablets. They were then reassessed using the MDS-UPDRS-III when found to be in their clinically defined ON medication state (when the patient noted they were ON, usually approximately 45–60 min after levodopa is given).

Statistical analysis

The open-source R software environment (R Core Team, 2018, version 3.4.4; Available from: www.R-project.org/.) was used for all statistical analyses performed. All data were tested for normality using the package rstatix (v0.6.0),

analysis of variance was performed using the package afex (v0.28–0), and pairwise comparisons were performed with the package emmeans (v1.5.3). A repeated measures two-way ANOVA followed by Tukey's multiple comparisons was used for Fig. 1. A one-way ANOVA followed by Tukey's post hoc multiple comparisons test was used for Figs. 2 and 3. The significance threshold was set at $p < 0.05$ for all statistical analyses performed. Values are expressed as Mean ± SD unless otherwise stated.

Results

Of the sixty-five participants included in the study, 17 were in group 1 (2–5 years), 17 in group 2 (6–9 years), 19 in group 3 (10–13 years) and 12 in group 4 (more than 14 years). The demographic variables and clinical profile of each group are highlighted in Table 1. OFF motor scores were high at each stage of disease duration, beginning

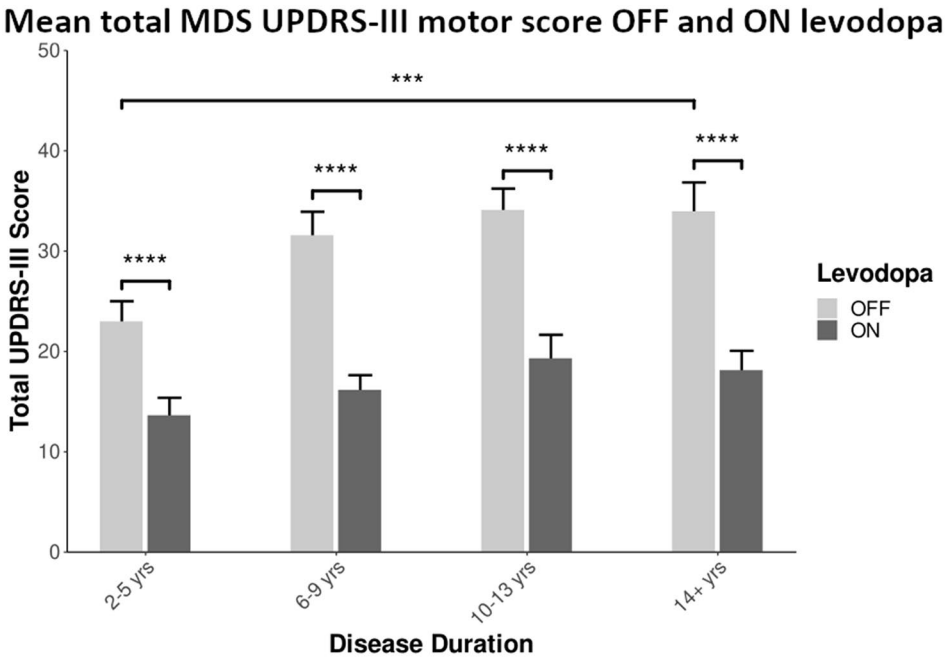

Fig. 1 OFF motor scores increase significantly after 14 years of disease while ON motor scores remain relatively stable. There was a statistically significant difference between MDS UPDRS-III scores OFF and ON Levodopa at 2–5 years ($N = 17$, $P < .001$****), 6–9 years ($N = 17$, $P < .001$****), 10–13 years ($N = 19$, $P < .001$****), and 14+ years ($N = 12$, $P < .001$****). A significant interaction was also observed between disease duration of 2–5 years and 14+ years OFF levodopa ($P = .030$***). Repeated measures two-way ANOVA and Tukey's multiple comparisons were conducted. Results are reported as the Mean ± SEM

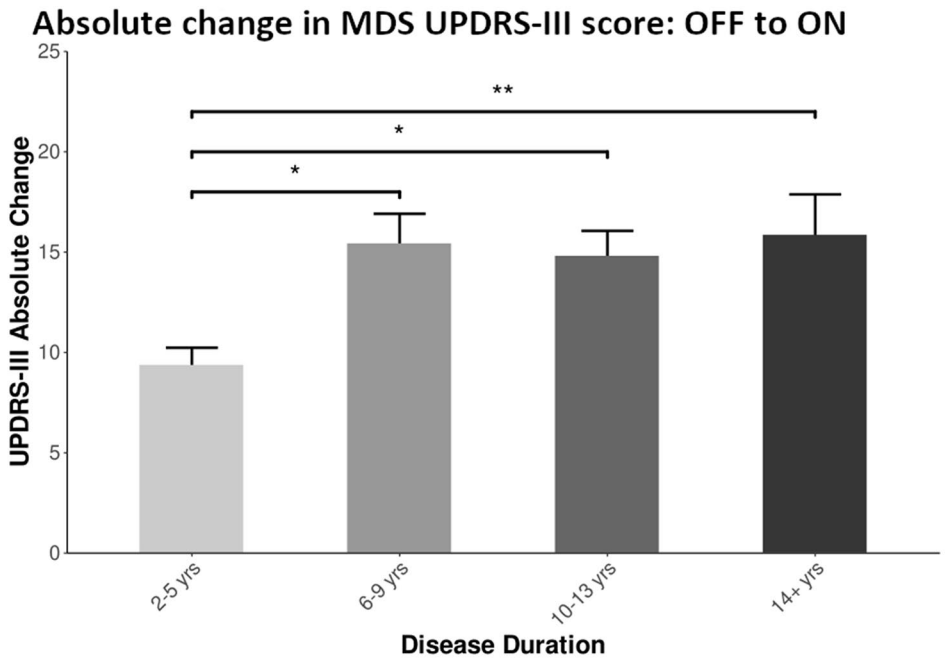

Fig. 2 Absolute change in UPDRS-III scores from OFF to ON levodopa across disease duration groups. The levodopa response initially widens and then plateaus in later stages of disease duration. A one-way ANOVA followed by Tukey's post-hoc test revealed a significant difference between Groups 2–5 years and 6–9 years ($P = .016$*), 2–5 years and 10–13 years ($P = .031$*) and 2–5 years and 14 + years ($P = .010$**). Results are reported as the mean ± SEM

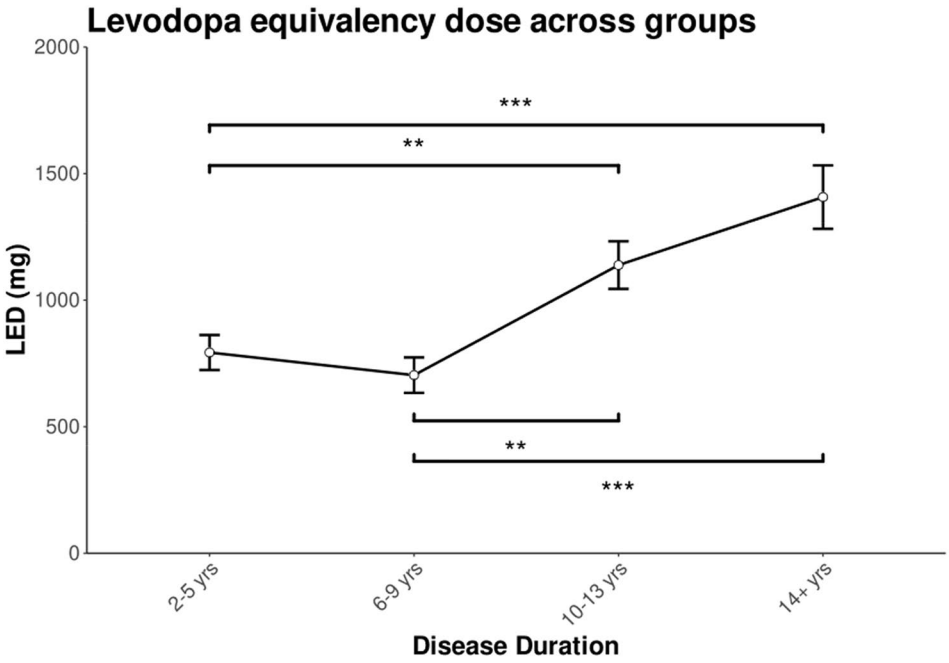

Fig. 3 Mean daily levodopa equivalency dose significantly increases after 9 years of PD. A significant difference was revealed between Groups 2 and 5 years ($N=17$) and 10–13 years ($N=19$) ($P=.031$**), and between Groups 2 and 5 years and 14 + years ($N=12$) ($P<.001$***). A significant difference was also observed between Groups 6 and 9 years ($N=17$) and 10–13 years ($P=.003$**) and between Groups 6 and 9 years and 14 + years ($P<.001$****). Results are reported as the mean ± SEM. A one-way ANOVA followed by Tukey's post hoc multiple comparisons test was completed. *LED* levodopa equivalency dose in milligrams

Table 1 Patient demographics

	PD 2-5 yrs (N = 17)	PD 6-9 yrs (N = 17)	PD 10-13 yrs (N = 19)	PD 14+ yrs (N = 12)
Age (Years)	62.24 ± 7.60	65.41 ± 6.61	66.79 ± 7.66	66.08 ± 6.10
Sex: Female, %(n)	5 (29.41%)	5 (29.41%)	5 (26.32%)	6 (50.00%)
PD Duration (Years)	4.41 ± 0.80	7.32 ± 0.88	11.11 ± 0.99	16.08 ± 1.44
Levodopa Duration (Years)	3.41 ± 1.37	5.68 ± 1.93	8.95 ± 2.68	13.58 ± 3.00
LED (mg)	793.18 ± 285.08	703.68 ± 288.76	1,138.53 ± 409.51	1,407.17 ± 434.13
UPDRS OFF	22.94 ± 8.52	31.53 ± 9.87	34.05 ± 9.50	33.92 ± 10.15
UPDRS ON	13.59 ± 7.40	16.12 ± 6.26	19.26 ± 10.45	18.08 ± 6.86
aLR OFF-ON	9.35 ± 3.64	15.41 ± 6.19	14.79 ± 5.54	15.83 ± 7.08

* LED = levodopa equivalency dose;UPDRS = Unified Parkinson's Disease Rating Scale; aLR = Absolute levodopa response.

at 22.94 ± 8.52 and then increasing to 31.53 ± 9.87, 34.05 ± 9.50, and 33.92 ± 10.15 points in groups 1, 2, 3, and 4, respectively. The difference in mean OFF scores between group 1 and group 4 was significant at 10.98 points ($P<0.001$) (Fig. 1). ON motor scores for groups 1, 2, 3, and 4 were 13.59 ± 7.40, 16.12 ± 6.26, 19.26 ± 10.45, and 18.08 ± 6.86, respectively, with no statistically significant difference between groups. When comparing the OFF and ON scores at each stage of disease duration, a significant response to medication was maintained at all stages of disease ($P<0.001$) (Fig. 1).

Absolute levodopa response (aLR) was calculated as the difference in means from OFF to ON stage (Fig. 2). The aLR in group 1 (9.35 ± 3.64) was significantly less in comparison with group 2 (15.41 ± 6.19, $P=0.016$), group 3 (14.79 ± 5.54, $P=0.031$), and group 4 (15.83 ± 7.08, $P=0.010$). The aLR appears initially to rise and then plateaus after 5 years of disease.

The mean levodopa equivalency dose in groups 1, 2, 3, and 4 was 793.18 ± 285.08 mg, 703.68 ± 288.76 mg, 1138.53 ± 409.51 mg, and 1407.17 ± 434.13 mg, respectively. Mean LED in group 1 was significantly less than both

group 3 ($P=0.031$) and group 4 ($P<0.001$). Mean LED in group 2 was also found to be significantly less than group 3 ($P=0.003$) and group 4 ($P<0.001$). Also, the mean LED in group 2 was lesser that group 1 though the difference was not statistically significant. Hence, after approximately 9 years of disease, a large increase of ~ 350 mg in LED was seen (Fig. 3) without a significant increase in OFF motor score. By 14 + years of disease, mean LED increased by an additional 269 mg, producing a total 703 mg difference between groups 2 and 4.

Discussion

In this study, LCT showed that the OFF scores increased with the disease duration but the improvement in the ON scores was substantial in all groups as well and was seen despite the disease progression. In addition, there was a significant difference in the LED for the first nine years of the disease and thereafter. The 30% cut-off during the LCT was seen in all groups and hence, does not appear to be the sole requirement for selecting patients for neuromodulation with DBS. Our findings are slightly different from Clissold et al. where the levodopa motor response increased for the first five years of treatment and then declined in 'off–on' scores in parallel [18]. They followed the same cohort over more than a decade while the present study had a group of PD patients at different disease durations. It is quite possible that the worsening axial and non-levodopa responsive symptoms as the disease progressed caused an increase in the 'off–on' scores in their study.

LCT is a useful clinical exercise to exclude atypical parkinsonian syndromes, defining levodopa unresponsive symptoms and predicting the surgical response [19]. However, tremor dominant PD and those with prominent dyskinesias do respond to DBS despite a poor response on LCT [19, 20]. Based on the observations during the LCT, two patient phenotypes emerge: (A) patients that still experience LDR, and (B) patients who no longer experience LDR. Clinical features of phenotype A were lower doses of levodopa, a good 'on' response, moderate 'off' scores and the difference between 'off' versus 'on' scores was smaller (groups 1 and 2 match phenotype A). In comparison, clinical features of phenotype B were substantially higher levodopa dose, much worse 'off' scores, and an equivalent improvement in 'on' compared with phenotype A, making the 'off–on' score difference even higher than in the early-stage groups. The change from LDR to SDR represents an important transition in the progression of PD both in terms of symptomatic management, state of neurodegeneration and in making critical management decisions such as DBS. Nutt et al. have demonstrated that as the disease advances, the magnitude of SDR increases and compensates for the falling LDR. Thus, there is an inverse correlation of the LDR with the SDR [21]. These transitions are known to take several years, usually 7–9 years of disease and in appropriate patients are the main reason why advanced therapies such as DBS are utilized. This conversion from LDR to predictable and then to unpredictable fluctuations may represent a change in how levodopa is metabolized, switching from nigral to non-nigral systems [10, 11]. Degeneration of the dopaminergic neurons was pathologically seen in the postmortem PD patient brains by Kordower et al. The dopamine markers in the fibers of PD dorsal putamen were variably reduced in the initial four years and virtually absent thereafter [22]. This further supports our notion of switch over from nigral to non-nigral systems quite early in the PD timeline. Early intervention, with advanced therapy such as DBS, may be especially important in those patients that are transitioning from the stable LDR state into unpredictable fluctuations (disease duration of 6–9 years in the present study). Interestingly, it was observed that a significant increase in LED between group 2 and group 3 (Fig. 1) was not reflected in UPDRS-OFF scores (Fig. 3). Although not statistically significant, the LED in group 2 was slightly less than that in group 1. We postulate that at this stage, the LDR has just started to wane and the extra-nigral system would soon start to compensate for the progressive dopaminergic degeneration. The CAPSIT-PD protocol recommends PD patients not be considered for DBS surgery until at least 5 years of disease duration [7]. Volkmann et al. reported that of the 122 candidates who received the implanted DBS device, average disease duration at time of surgery was 14.2 years [23]. Our observations suggest that it may be possible to identify patients with these phenotypic differences quite early in the timeline by carefully observing those patients that begin to exhibit phenotype B. The increase in levodopa requirements is clinically obvious but the transition of having a much worse 'off', yet having a very good 'on' response, requires an 'off–on' LCT. Given the importance of this transition, it may be worthwhile to do routine LCT beginning when the patient's dose requirements begin to increase. In this scenario, if the 'off' versus 'on' state shows a significant difference in the UPDRS score, then one might suspect that the patient may be beginning to show the transition into unpredictable fluctuations and hence mainly non-nigral dopamine metabolism. This could serve as a potential method of considering such patients for advanced therapies including DBS.

Early DBS intervention could theoretically delay the switch to an extra-nigral control system by reducing the workload of the surviving nigral system early on. As theorized, stimulating in areas, such as the STN or GPi, reduces the workload of the surviving nigrostriatal dopaminergic neurons in the PD brain. In their study on 30 patients with subthalamic DBS, Wider et al. showed that subthalamic DBS compensates for the SDR and LDR in PD patients [24].

Similarly, Moro et al. demonstrated the benefits of bilateral subthalamic DBS in 28 PD patients. They concluded that DBS, along with reduction in levodopa dosage after surgery, modulates the SDR and induces long-term plastic changes responsible for the clinical benefits in PD patients [25].

This study has a few limitations. First, we would have preferred to withhold the Parkinson's medications for a long time to produce a clinically 'real off' stage and not an overnight levodopa withdrawal. In ideal circumstances, this would best tell us about the magnitude of LDR. However, this was not practically feasible in patients on long-term levodopa therapy due to ethical considerations. Second, we selected a clinical tool which is quick and simple to use, the LCT on follow-ups, to determine the transition from LDR to SDR and hence a timely surgical intervention. We did not examine the duration of 'on' in these patients and it is quite possible that patients in stage 3 or 4 of our cohort had an SDR of a rather short duration, requiring frequent levodopa dosage. In these scenarios, the LED requirements should guide us to determine their disease advancement and those requiring an increase in their LED should be re-evaluated for an LCT and planned for DBS accordingly. We should have investigated the axial and appendicular scores on the LCT and that could have helped us segregate patients into suspected favorable or unfavorable outcomes. Axial symptoms not responsive to levodopa are a criterion for ineligibility for DBS and a note of axial scores and their response on levodopa challenge should always be made on LCT [26].

Conclusion

We theorize that in a state of gradual nigral cell death, extra-nigral control systems eventually take over to maintain a significant response. Rethinking the levodopa response may be necessary so that patients early in disease might be considered in the screening process for DBS. Individuals with early PD who have a minimal response to levodopa may be receiving significant motor benefit from the LDR and relying on a primarily nigral control system. Waiting for patients to switch to a poorly regulated extra-nigral control system characterized by further motor complications before initiating DBS may be too late. In the timeline of PD, when the symptoms advance, as seen by increased LED and fluctuations, it is worth doing an LCT at regular follow-ups to determine waning LDR which could be the time for implementation of neuromodulation with DBS.

Authors' contributions All authors contributed to study conception and design. Material preparation and data collection were carried out by MP. The first draft of the manuscript was prepared by DK, GG. The writing – review and editing was done by DK, GG and MJ. The study was carried out under the supervision of MJ.

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Availability of data and material The data are available on request submitted to the institutional ethics committee.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethics statement The study was approved by the institutional ethics committee and has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments (REB #107253).

Consent to participate An informed consent was obtained from all patients included in the study.

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