Levodopa Responsiveness of Freezing of Gait: Results Using a Levodopa Test

S.A. Factor[1], G. Alexander[1], B. Sommerfeld[1], D. Bernhard[1], J. L. McKay[2], J. Hanfelt[3], S. John[1], F. C. Goldstein[1]

[1] Jean & Paul Amos PD & Movement Disorders Program Department of Neurology, Emory University

[2]Wallace H. Coulter Department of Biomedical Engineering, Georgia Tech and Emory University

[3]Emory University Department of Biostatistics and Bioinformatics

INTRODUCTION

• Freezing of gait (FOG) is among the most disabling and poorly understood motor features of Parkinson's disease (PD). It is a leading cause of falls, greatly interferes with ADL's, causes social isolation and poor quality of life (Nutt et al Lancet Neurol 2011).

• FOG appears to develop/progress independently of the other motor features, is associated with specific risk factors, and is thought to be caused by specific as yet unknown pathology (Factor et al JNNP 2011).

• FOG is often considered to be untreatable/non-dopaminergic. However, some cases are levodopa responsive, but the responsiveness is heterogeneous and poorly understood.

• There are at least three pharmacologic subtypes of FOG:

- "off" or responsive FOG which is present in the un-medicated state, and disappears with levodopa therapy
- "on" FOG which is brought on by levodopa; disappears when the medication wears off
- unresponsive FOG is present in "off" & "on" states (Espay et al Neurol 2012)

•There is evidence these subtypes are pathophysiologically different (Factor et al PRD 2014).

The purpose of the study was to examine the nature of levodopa responsiveness of FOG using a levodopa test paradigm.

METHODS

Study Population

All participants were selected from the Emory Movement Disorders clinic and provided written informed consent according to procedures approved by Emory University IRB.

Inclusion criteria for all participants:

1. Diagnosis of PD by United Kingdom Brain Bank criteria
2. Hoehn & Yahr stage I-IV
3. Levodopa treated and responsive
4. Able to manage a 12 hour "off" dopaminergic medication state
5. Age 18-80 years

Exclusion criteria for all participants:

1. Atypical parkinsonism: PSP, MSA, CBD, VP
2. Prior treatment with medications that cause parkinsonism
3. Stage V PD –unable to walk independently when off
4. Absence of levodopa response
5. Neurological or orthopedic disorders interfering with gait
6. Dementia precluding completing study protocol

Additional inclusion criteria for participants with FOG:

1. FOG noted in medical history/confirmed by examiner

Levodopa Test Paradigm

Clinical and demographic data collection. All patients came to clinic in the practically defined "off" state defined as 12 – 16 hours off medications. We recorded demographics, Levodopa Equivalent Doses (LED), FOG duration, NFOG-Q, MDS-UPDRS and MoCA.

"Off" state data collection and motor examination

• Orthostatic blood pressures (5 minutes lying down, 1 minute standing)
• Blood drawn for serum levodopa level (measured by HPLC)
• MDS-UPDRS part III (conducted by SAF)
• Motion capture evaluation (to be reported separately)
• Timed up and go (TUG) 4-7 meter. The patients stand from the seated position, walk the distance, turn 180 degrees walk back and sit down.
•Three scenarios 3 times each:

- Normal walking speed
- Normal speed carrying a tray with cups, dual tasking
- Normal speed completing a cognitive task (serial 3's)
- 360 degree turns 2 times each direction

Levodopa administration

• All patients were administered a levodopa dose adequate to achieve a full "on" state.

"On" state data collection and motor examination

• "Off" state procedures were repeated during full "on" state.
• The interval between "off" and "on" testing varied from 30 minutes to 3 hours.

Analytic plan

• Patients were classified as responsive (RFOG: defined as FOG only during "off" time), unresponsive FOG (URFOG: defined as any FOG during the "on" time) or no FOG (NOFOG) according to changes between the "off" and "on" states during administration of the MDS UPDRS-III and TUGs.
• We compared the 3 groups for demographic, motor features of PD (including change of exam from "off" to "on" state, LED, and levodopa levels.
• Differences in study variables between the RFOG, URFOG, and NOFOG groups were evaluated with tests of central tendency (continuous variables: independent samples t-tests or ANOVA with Tukey post-hoc tests; frequency variables: chi-squared/Fisher tests).

RESULTS

Demographics and FOG measures for the three groups

55 subjects were enrolled and tested: 16 RFOG, 22 URFOG, 17 NOFOG. See Table 1 for demographics. The only difference between groups was PD duration which was shorter for NOFOG than the other groups. There were no patients with "on" FOG induced by medication. We also recorded FOG duration, age of onset FOG and N-FOGQ. The N-FOGQ score was higher (more severe) in the URFOG group compared to the RFOG group.

Levodopa Dose

The daily LED doses were significantly different between groups (Table 2). LED for the levodopa test was 40% higher than the standard morning dose and produced a full on in all patients (Table 2). 75% of the RFOG patients developed dyskinesia compared to > 50% of those in the URFOG and NFOG groups. Levodopa levels increased commensurate with dosing (Table 2; Figure 1).

MDS-UPDRS Part 3 Motor Scores:

Were similar for all 3 groups in the off state. The URFOG group had a higher score than the other groups when "on" but the change overall with levodopa was not significantly different (Table 3; Figure 2). Of the individual items in the part 3 score, item 4 (Foot tapping) and item 11 (Freezing) was the main difference (Figure 3). Postural instability score item 12 was higher in the URFOG group but the change was not significantly different between groups (Figure 3).

Table 1. Demographics and patient completed FOG related measures of patients with levodopa responsive FOG (RFOG), levodopa unresponsive FOG (URFOG) or no FOG (NOFOG). [a]N=53. [†]Common superscripts indicate significant differences between the marked groups.

Characteristic	RFOG N=16	URFOG N=22	NOFOG N=17	P Value
Age (y)	67±6 [55–76]	70±7 [56–81]	67±12 [39–82]	0.40
Sex				0.27
Male	13 (81)	19 (86)	11 (65)	
Female	3 (19)	3 (14)	6 (35)	
Education (y)	18±4 [12–27]	16±3 [9–20]	17±1 [14–20]	0.18
MoCA[a]	25±4 [18–30]	23±5 [10–30]	26±4 [16–30]	0.07
PD duration (y)	10±5 [3–23]	11±8 [0–25][†]	6±4 [0–13][†]	0.04
Age at onset (y)	58±8 [43–72]	60±12 [38–80]	61±13 [34–79]	0.70
FOG duration (y)	3±3 [0–10]	3±3 [0–12]		0.82
Age at FOG onset (y)	64±7 [53–76]	67±7 [51–80]		0.22
NFOG-Q (points)	17±6 [6–25][†]	22±3 [16–28][†]		<0.01

Table 2: LED doses and levodopa levels of patients with levodopa responsive FOG (RFOG), levodopa unresponsive FOG (URFOG) or no FOG (NOFOG). aN=53. †Common superscripts indicate significant differences between the marked groups.

Characteristic	RFOG N=16	URFOG N=22	NOFOG N=17	P Value
LED (mg)				
Daily	1255±494 [399–2046]	1571±731[†] [798–3908]	833±303[†] [399–1505]	<0.001
Morning	253±99 [133–426]	337±147[†] [133–665]	231±88[†] [133–413]	0.02
Challenge	416±293 [133–1348]	460±252 [133–1330]	292±132 [133–532]	0.09
Serum LD (ng/mg)				
OFF[a]	0.4±0.3 [0.0–0.9]	1.2±2.0 [0.0–7.2]	0.1±0.2 [0.0–0.5]	0.05
LD Challenge[a]	28.0±10.3 [13.5–49.6]	40.3±26.8 [12.9–113.3]	25.4±19.0 [7.9–75.1]	0.07

Table 3: MDS-UPDRS score scores in each group of patients with levodopa responsive FOG (RFOG), levodopa unresponsive FOG (URFOG) or no FOG (NOFOG).

Characteristic	RFOG N=16	URFOG N=22	NOFOG N=17	P Value
MDS UPDRS-III Total				
OFF	30±10 [16–46]	35±11 [20–57]	31±13 [13–57]	0.32
LD Challenge	16±7 [8–31][†]	25±10 [7–47][†]	18±15 [4–53]	0.04
Change	15±8 [4–33]	11±11 [-4–41]	12±7 [-4–28]	0.42
MDS UPDRS-III.11, Freezing				
OFF	1.9±0.7 [1–3]	2.3±1.3 [0–4]		0.23
LD Challenge	0.1±0.3 [0–1][†]	1.6±1.2 [0–4][†]		<0.001
Change	1.8±0.8 [1–3][†]	0.8±1.7 [-4–4][†]		0.03
MDS UPDRS-III.12, Postural Instability				
OFF	0.3±0.8 [0–3]	1.1±1.4 [0–4]	0.3±0.8 [0–3]	0.04
LD Challenge	0.0±0.0 [0–0]	0.5±1.0 [0–3]	0.1±0.2 [0–1]	0.06
Change	0.3±0.7 [0–3]	0.6±0.9 [0–3]	0.2±0.6 [0–2]	0.25

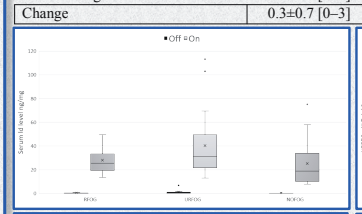


Figure 1. Serum levodopa levels corrected for protein levels pre and post levodopa test.

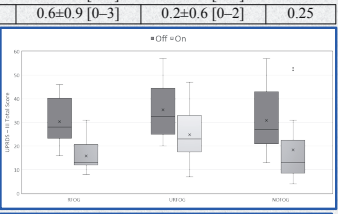
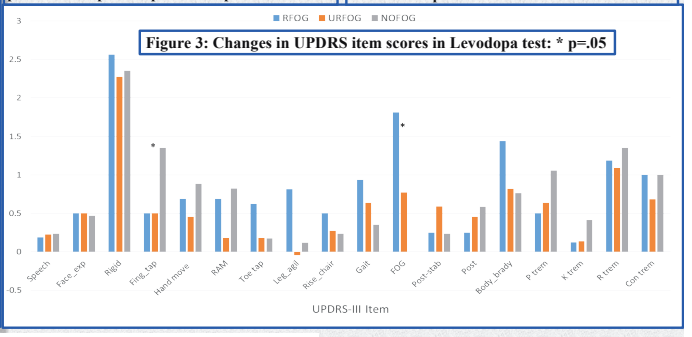


Figure 2: MDS-UPDRS part 3 total score changes in the levodopa test.



CONCLUSIONS:

• The levodopa test elevated levodopa serum levels appropriately and resulted in a full "on" state in all patients.
• The levodopa test demonstrated the heterogeneity of levodopa response for FOG with a group that responds completely and has no FOG in the "on" state and an "unresponsive" group that continues to have FOG in the "on" state.
• The URFOG Group has more severe FOG than RFOG (N-FOGQ). It also has a longer duration of PD and uses a higher daily LED.
• All groups responded to levodopa overall. The URFOG group was a continuum of some patients with partial response of FOG to levodopa and some with no response.
• Could it be that RFOG and URFOG are separate phenomena that can occur alone or in combination (explaining those with partial response) or is there a continuum from totally responsive to partially responsive to non-responsive over time? A longitudinal study will be needed to address this question.

FUNDING:
Curtis family Fund
Sartain Lanier Family Foundation
American Parkinson's Disease Association
NIH K25 HD086276