levodopa responsiveness of freezing of gait: results using a levodopa test

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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 ADLs, causes social isolation and poor quality of life (Nutt et al. Lancet Neurol 2011).

FOG appears to develop progressively independent 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 NINDS 2011). FOG is often considered to be unresponsive/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 unmedicated state, and disappears with levodopa therapy
  - "on" FOG which is brought on by levodopa; disappears when the medication wears off
  - "off" or "on" FOG states not defined by Nutt et al Neurol 2012

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

The purpose of this 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 1-4
3. Levodopa treated and responsive
4. Able to manage a 12 hour "off" dopaminergic medication state
5. Age >18 years

Exclusion criteria for all participants:
1. Atypical parkinsonism: PSP, MSA, CBD, WP
2. Prior treatment with medications that cause parkinsonism
3. Stage 4 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 to the practically defined "off" state defined as 12 − 16 hours off medication. We recorded demographics, levodopa Equivalent Doses (LED), FOG duration, NFOG-Q, MDS-UPDRS III and MoCA.

"LED" 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 (computed by SAP)
• 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, then return to the seated position within 15 seconds.
• 360 degree turns 2 times each

Levodopa administration:
• All patients were administered a levodopa dose adequate to achieve a full "off" state.
• "On" state data collection and motor examination.

"Off" state procedures were repeated during "full" "off" state.
• The time interval between "off" and "on" testing varied from 30 minutes to 2 hours.

Analytic plan:

• Patients were classified as response (RFOG) defined as FOG only during "off" times, unresponsive FOG (URFOG) defined as FOG during any "on" or "off" times) or no FOG (NFOG) according to changes between the "off" and "on" states during administration of the MDS-UPDRS III and TUG.
• 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 NFOG groups were evaluated with tests of central tendency (continuous variables: independent samples t-tests or ANOVA with post hoc Bonferroni correction).

RESULTS

Demographics and FOG measures for the three groups

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

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

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 responsiveness for FOG with a group that responds completely and has no FOG in the "off" state and an "unresponsive" group that continues to have FOG in the "on" state.
• The RFOG group has a more severe FOG than RFOG. 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 (repeating 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.

Table 1. Demographics and patient completed FOG related measures of patients with levodopa responsive FOG (RFOG), levodopa unresponsive FOG (URFOG) or no FOG (NFOG).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RFOG</th>
<th>URFOG</th>
<th>NFOG</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>67±8</td>
<td>55±6</td>
<td>67±2</td>
<td>0.40</td>
</tr>
<tr>
<td>Male</td>
<td>13 (81)</td>
<td>19 (66)</td>
<td>11 (65)</td>
<td>0.27</td>
</tr>
<tr>
<td>Female</td>
<td>3 (19)</td>
<td>1 (14)</td>
<td>6 (35)</td>
<td></td>
</tr>
<tr>
<td>Duration (y)</td>
<td>16±1</td>
<td>12±2</td>
<td>17±1</td>
<td>0.18</td>
</tr>
<tr>
<td>MoCA*</td>
<td>25±4</td>
<td>18±3</td>
<td>23±5</td>
<td>0.07</td>
</tr>
<tr>
<td>PD duration (y)</td>
<td>10±5</td>
<td>8±3</td>
<td>6±4</td>
<td>0.04</td>
</tr>
<tr>
<td>Age at onset (y)</td>
<td>58±8</td>
<td>43±7</td>
<td>50±12</td>
<td>0.70</td>
</tr>
<tr>
<td>FOG duration (y)</td>
<td>12±3</td>
<td>12±3</td>
<td>12±1</td>
<td>0.82</td>
</tr>
<tr>
<td>Age at FOG onset (y)</td>
<td>64±7</td>
<td>53±5</td>
<td>67±5</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Table 2: LED doses and levodopa levels of patients with levodopa responsive FOG (RFOG), levodopa unresponsive FOG (URFOG) or no FOG (NFOG).

<table>
<thead>
<tr>
<th>Characteristic</th>
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<th>URFOG</th>
<th>NFOG</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily LED (mg)</td>
<td>125±9</td>
<td>157±31</td>
<td>83±30</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Morning LED (mg)</td>
<td>399±204</td>
<td>398±300</td>
<td>399±120</td>
<td></td>
</tr>
<tr>
<td>Challenge</td>
<td>416±29</td>
<td>402±252</td>
<td>292±132</td>
<td>0.09</td>
</tr>
<tr>
<td>Serum LD (mg/ml)</td>
<td>133±124</td>
<td>139</td>
<td>133±52</td>
<td>0.005</td>
</tr>
<tr>
<td>OFF*</td>
<td>4.0±0.3</td>
<td>1.0±0.2</td>
<td>4.0±0.3</td>
<td>0.05</td>
</tr>
<tr>
<td>LD Challenge</td>
<td>28.0±10.3</td>
<td>40.3±6.8</td>
<td>24.0±19.0</td>
<td>0.07</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RFOG</th>
<th>URFOG</th>
<th>NFOG</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS-UPDRS III Total</td>
<td>0.9±1</td>
<td>2.0±2</td>
<td>1.0±2</td>
<td>0.32</td>
</tr>
<tr>
<td>MDS-UPDRS III, Freezing</td>
<td>1.0±0</td>
<td>0.0±0</td>
<td>1.0±0</td>
<td>0.001</td>
</tr>
<tr>
<td>MDS-UPDRS III, Postural Instability</td>
<td>1.0±0</td>
<td>0.0±0</td>
<td>1.0±0</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 4: Changes in UPDRS item scores in Levodopa test.

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.

Figure 3: Changes in UPDRS item scores in Levodopa test: * p<0.05