Is Freezing of Gait in Parkinson’s Disease Related to Asymmetric Motor Function?

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Freezing of gait (FOG) is a disabling phenomenon common in patients with advanced Parkinson’s disease (PD). The cause of FOG is unclear. The objective of this study was to explore a novel hypothesis stating that FOG is related to asymmetric motor performance. We compared PD patients that experience FOG episodes (PD/FOG) with PD patients that do not (PD−FOG) and studied the relationship of FOG to asymmetry in gait and in rhythmic hand movement performance to determine whether potential FOG-related gait asymmetry is unique to walking or whether it is systemic. Subjects were tested in an “off” (unmedicated) and again in an “on” (medicated) state. Gait was more asymmetric in PD+FOG than in PD−FOG during “off” state ($p = 0.005$) and during “on” ($p = 0.016$). Rhythmicity of foot swing in one leg was correlated with the other leg in PD−FOG but not in PD+FOG. There was no difference in asymmetry in performance of rhythmic hand movements between the two groups. No correlation was found between asymmetry of clinical symptoms and gait asymmetry. Taken together, the results of this study suggest that bilateral uncoordinated gait and marked gait asymmetry, but not asymmetry in motor performance in general, are associated with FOG.

Freezing of gait (FOG) is a debilitating phenomenon that is common among patients with advanced Parkinson’s disease (PD).1–4 FOG is typically a paroxysmal event that unexpectedly “attacks” the subject at the start of walking, during turning, and even while walking in an unobstructed “open” runway.5 Previous studies have suggested that the pathophysiology of FOG may be distinct from those that lead to other parkinsonian symptoms. For example, no correlation was found between the frequency of FOG episodes and other motor symptoms of PD (eg, rigidity, bradykinesia), whereas FOG frequency was inversely correlated with tremor.3,6 These findings underscore the fact that FOG is the expression of pathophysiology that has yet to be fully explained.1,7

Few studies examined the mechanisms that underlie FOG. Yanagisawa and colleagues studied electromyographic (EMG) activity of leg muscles in PD patients with “frozen gait.”8 In these patients, they observed “unique but not uniform patterns of EMG” and suggested that rhythmic contraction of leg muscles beyond a certain rate is a factor in causing FOG. A low number of PD patients with freezing (n = 5) and incomplete description of the pathological EMG pattern, presumably characterizing FOG episodes, however, weaken the strength of their conclusions. Nieuwboer and her colleagues found that the strides performed just before FOG are characterized by decreasing stride length (with stable cadence) and suggested that failure to time and control the sequence of gait cycles causes a diminishing stride length which, in turn, leads to freezing.9 Hausdorff and colleagues found that gait of PD patients who experience FOG (PD+FOG) is characterized by increased stride-to-stride variability as compared with PD patients who do not experience freezing (PD−FOG).10 Thus, it was speculated that perhaps increased stride-to-stride variability and FOG fall on a continuum, the former being a mild and the latter being an extreme expression of dyscontrol. More recently, it has been observed that the timing of EMG activity of leg muscles was abnormal during the steps just before FOG episodes.11 These findings indicate irregular central timing mechanisms of muscle activation before freezing.

In this investigation, we address an aspect of gait that was not considered in previous studies of FOG: the role of bilateral coordination between the legs during gait. Several factors led us to examine this question. First, if impairment in the timing and pacing of movement that involves both legs takes place, as in FOG, an

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Received Oct 7, 2004, and in revised form Feb 18, 2005. Accepted for publication Feb 27, 2005.

Published online Apr 25, 2005, in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.20452

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impaired coordination of sequencing and timing of the activation of each leg may contribute to the deficiency. Second, a few investigations describe empirical evidence supporting the notion of asymmetric motor performance in FOG. For example, Abe and colleagues studied lower limb pedaling in PD patients. Although the relative phase (between the legs) was locked at approximately 180 degrees in healthy elderly and some of the PD patients, PD+FOG patients exhibited relative phase drift monotonously from 0 to 360 degrees or an irregularly modulated phase. Based on these studies, we hypothesized that FOG may be a manifestation of asymmetrical and uncoordinated bilateral motor performance of gait. To test this hypothesis, we studied the asymmetry of gait in PD+FOG and PD−FOG. To determine whether any potential FOG-related differences in gait asymmetry were unique to walking or if they were part of more general motor control disturbance, we also studied the relationship between FOG and symmetry of rhythmic motor performance in the upper extremities.

Subjects and Methods

Subjects

Subjects were recruited from the outpatient clinic of the Movement Disorders Unit at Tel Aviv Sourasky Medical Center. The subjects were referred by their regular treating neurologist who had been informed of the inclusion and exclusion criteria. The patients then were interviewed by the neurologists of the research team (N.G. and Y.B.) who confirmed suitability. The subjects were patients with idiopathic PD, as defined by the UK Brain Bank criteria, were receiving 1-dopa treatment, experienced motor response fluctuations, and had a Hoehn and Yahr score less than 4 while in an “off” state (ie, at least 12 hours off antiparkinsonian medications). PD subjects were excluded if they had brain surgery in the past or if they had clinically significant comorbidities likely to affect gait including diabetes mellitus, rheumatic or orthopedic disease, dementia (score of the Mini-Mental State Examination [MMSE] < 25), depression, or history of stroke, as determined by clinical or radiological evaluation. Each patient was classified as either PD+FOG or PD−FOG subject, based on his/her responses to the FOG questionnaire (question 3).

Clinical characteristics and a comparison of the variability of gait between PD+FOG and PD−FOG have been reported previously for a subset of these patients. The experimental protocol was approved by the Human Studies Committee of the Tel Aviv Sourasky Medical Center. All subjects provided informed written consent according to the Declaration of Helsinki before entering the study.

Motor and Cognitive Evaluation

Patients were first assessed in the morning, during the “off” state. The assessment during the “off” state included: (1) gait (as described below); (2) part III (the motor portion) of the Unified Parkinson’s Disease Rating Scale (UPDRS); and (3) timed motor tests of the Core Assessment Program for Intracerebral Transplantations (CAPIT). To summarize CAPIT performance, we measured and summed for each hand the times required for 20 complete cycles of alternating taps of the palm and dorsum of the hand, for 20 successive taps of 2 points 30 cm apart, and for tapping the thumb to each finger in succession (10 repetitions). The hand with the higher sum was identified, and the sum was marked as total high (TH). The lower sum was marked as total low (TL).

Walking Protocol

Subjects were instructed to walk at their normal pace on level ground for a total of 80 m. Force-sensitive insoles were placed in the subjects’ shoes. Two sensors are embedded in each insole, one under the heel and the other under the balls of the feet and the toes. The data from both sensors were combined before the recording. The recorded output was a time series (sampled at 300 Hz) of the vertical ground reaction force. Measurements from both feet were synchronized.

A more complete description of the measurement system was provided earlier. Temporal gait parameters were determined using off-line computerized analysis of the force signal, which identified initial contact of the foot with the ground (“heel strike”) and then, the departure of the foot from the ground (“toe off”) for each stride, as previously described. To focus on the assessment of the dynamics of continuous “normal” walking, we excluded gait segments that include freezing episodes and turns from the analysis, as described previously.

Gait and Asymmetry Parameters

The focus of this study was on the assessment of asymmetry and bilateral coordination of gait; thus, gait parameters were evaluated for each foot separately. The following parameters were determined:

- **Left swing time**: the time the left foot was in the air, averaged across all strides
- **Right swing time**: the time the right foot was in the air, averaged across all strides
- **Left swing variability**: the coefficient of variation (CV; $CV = 100 \times \text{standard deviation/mean}$) of the left swing time
- **Right swing variability**: CV of the right swing time
- **Short and long swing time**: $\text{SSWT}$ and $\text{LSWT}$, respectively
- **Gait asymmetry**: We defined gait asymmetry as follows: gait asymmetry = $|\ln(\text{SSWT}/\text{LSWT})|$
- **CAPIT asymmetry** was defined as follows: CAPIT Asymmetry = $|\ln(\text{TL}/\text{TH})|$
- **UPDRS asymmetry**: for each side of the body, we calculated the sum of scores of UPDRS items 20 to 26 (these items refer to rest tremor, action or postural tremor, rigidity, finger taps, hand movements, rapid alternating movements
of the hands and leg agility, respectively). UPDRS asymmetry was defined as the ratio: (higher sum – lower sum)/
(higher sum + lower sum).

Statistical Analysis
To study the effect of Group (PD+FOG and PD−FOG), the effect of medication intake (“off” and “on” states), and
the Group*Medication interaction, we applied a mixed effect model (Proc Mixed-SAS software, SAS, Cary, NC) on each
of the following dependent parameters: gait asymmetry, CAPIT asymmetry, SSWT, LSWT, SSWCV and LSWCV.
Values used in the model were within subject means. The model takes into account the “repeated” nature of the design
and accounts for missing values in the data set. For each dependent variable, we applied a separate model. A repeated
measures model was applied because each subject was evaluated twice, during the “off” and “on” states. We used a
mixed effect model, because Group is a fixed factor and “subject” is a random factor. Correlations between different
parameters were assessed by Spearman’s ρ coefficient. A ρ value of less than or equal to 0.05 (two sided) was considered
statistically significant.

Results
Data from 24 PD+FOG and 12 PD−FOG were studied. Subject characteristics of the two study groups
(PD+FOG vs PD−FOG) are described in Table 1. Mean values of age, Hoehn and Yahr scale, disease duration,
MMSE score, and score on UPDRS tests 20 to 26 were not significantly different between PD+FOG and PD−FOG.

Table 1. Clinical Characteristics of PD + FOG and PD-FOG Patients

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Age (yr) (mean ± SD)</th>
<th>Sex (M/F)</th>
<th>PD Duration (yr) (mean ± SD)</th>
<th>H&amp;Y “Off” (mean ± SD)</th>
<th>H&amp;Y “On” (mean ± SD)</th>
<th>UPDRS (#20–26) “Off” (mean ± SD)</th>
<th>UPDRS (#20–26) “On” (mean ± SD)</th>
<th>MMSE (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD − FOG</td>
<td>68.4 (7.4)</td>
<td>8/4</td>
<td>10.0 (4.0)</td>
<td>2.8 (0.4)</td>
<td>0.90</td>
<td>0.61</td>
<td>0.13</td>
<td>28.2 (2.3)</td>
</tr>
<tr>
<td>PD + FOG</td>
<td>63.1 (7.4)</td>
<td>17/7</td>
<td>10.4 (4.5)</td>
<td>3.0 (0.7)</td>
<td>2.7 (0.5)</td>
<td>21.9 (12.3)</td>
<td>10.0 (6.5)</td>
<td>27.8 (2.3)</td>
</tr>
<tr>
<td>p*</td>
<td>0.18</td>
<td>0.94a</td>
<td>0.80</td>
<td>0.29</td>
<td>0.016</td>
<td>0.001</td>
<td>0.001</td>
<td>0.933</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated: two-tailed t test. aχ².

PD = Parkinson's disease; FOG = freezing of gait; SD = standard deviation; H&Y = Hohen and Yahr scale; UPDRS = Unified Parkinson’s
Disease Rating Scale; MMSE = Mini-Mental State Examination.

Asymmetry in Gait Performance
Asymmetry of gait was larger in PD+FOG as compared with PD−FOG patients. Figure 1 demonstrates this point. Swing times are plotted for a series of strides during open runway walking. For the PD+FOG patient, left swing times and right swing times are clearly separated, whereas for the PD−FOG swing times from both feet overlap (ie, the pattern is largely symmetric). Thus, for the two subjects shown in Figure 1, a higher value of gait asymmetry is observed in the patient with FOG (0.37) as compared with the PD−FOG patient (0.02).

The mean value of gait asymmetry was significantly higher for the PD+FOG group in comparison with the PD−FOG group (Fig 2A). For both patient groups, gait tended to become more symmetric after the patients took their L-dopa medication (see Fig 2A), but this effect was not statistically significant. Differences in asymmetry between the two groups persisted in the “on” state (p = 0.016). The effect of medication intake on gait asymmetry was similar in both groups (ie, Group*Medication: p = 0.69).

Asymmetry in Repetitive Hand Movements
In contrast with what was observed for gait, asymmetry in upper extremity rhythmic performance was similar in PD+FOG and PD−FOG, both in the “off” and in the “on” states (see Fig 2B). As can be seen in Figure 2C, in the “off” state, there was no correlation between the values of gait asymmetry and the values of CAPIT asymmetry (Spearman’s ρ = 0.188; p = 0.319). During the “on” state, CAPIT asymmetry and gait asymmetry remained uncorrelated (Spearman’s ρ = 0.016; p = 0.933).

Comparison of Other Gait Parameters between Parkinson’s Disease with and without Freezing of Gait
Table 2 summarizes values of gait parameters from PD+FOG and PD−FOG during the “off” and “on” states for each leg. Gait dysrhythmicty, as expressed by SSWCV, was increased in PD+FOG as compared with PD−FOG during the “off” state (p < 0.001) and during the “on” state (p < 0.0001), with a nonsignificant Group*Medication interaction. Similar results were obtained for the LSWCV (see Table 2).

To gain additional insight into bilateral coordination of the pacing of motor commands to the legs, we studied the relationship between swing time variability seen in one leg and swing time variability in the second leg (Fig 3). Variability of one foot was related to the variability of the other foot in PD−FOG during the “off” state (see Fig 3A), but not in PD+FOG (see Fig 3B).
Gait Asymmetry and Asymmetry in Parkinson’s Disease Motor Symptoms (Unified Parkinson’s Disease Rating Scale asymmetry)

To assess whether gait asymmetry is related to asymmetry often seen in clinical symptoms of PD, we analyzed the correlation between UPDRS asymmetry and gait asymmetry. We found no correlation between gait asymmetry and UPDRS asymmetry for PD/H11001 FOG as well as for PD/H11002 FOG, both in “off” and “on” states (for all analyses: Spearman’s $\rho = 0.36$ and $p \geq 0.116$).

Discussion

Gait Asymmetry in Parkinson’s Disease with Freezing of Gait

A key finding of this study is that differences in swing times between the feet are higher in PD+FOG compared with PD−FOG (see Figs 1 and 2). Furthermore, unlike PD−FOG patients, in PD+FOG patients, variability in the right foot swing time is not correlated with variability in left foot swing time (see Fig 3A, B). We suggest that this disassociation between the left and the right swing CV indicates that variability (or conversely rhythmicity) in the timing of motor commands is independent for each leg in PD+FOG patients, but not in PD-FOG patients during the “off” state. Therefore, the hypothesis that FOG is related to asymmetric gait performance and reduced bilateral motor coordination of gait gains support from the results of this study. Our results do not necessarily point to a direct causal relationship between gait asymmetry, or between reduced bilateral coordination of gait, and the actual occurrence of FOG episodes; rather, they implicitly support this possibility.

One limitation of the study, however, is the relatively low number of PD-FOG patients. Despite this limitation, the consistency of the results during the “off” and the “on” states support our hypothesis.

The relation between gait asymmetry and FOG has not been reported previously to our knowledge. Asymmetry between the legs during gait in PD patients was reported by Miller and colleagues who compared EMG activity among PD patients and healthy elderly subjects.22 In these patients, motor fluctuations were not present, indicating relatively mild disease severity. Regardless, this finding can be considered supportive of the results of this study, because the gait asymmetry reported here also apparently exists to a smaller extent in patients in the early stages of the disease and even to a less extent in healthy elderly subjects.23 Thus, as in the case of stride time variability in which increased variability is also seen in PD patients as compared with healthy elderly subjects20 and the values of variability are even higher in PD+FOG,10 so too gait asymmetry may be considered as a progressive outcome of the disease.

Clinical Aspects

The effect of L-dopa intake on gait asymmetry and on swing times is consistent with its effect on gait rhythmicity.10 Hence it is suggested that these gait parame-
ters are directly influenced by dopamine levels in PD patients, most likely in concurrence with the higher rate of occurrences of FOG episodes during the “off” state.

It may be assumed that if uncoordinated gait and gait asymmetry play a role in the occurrence of FOG, or susceptibility among PD patients to FOG, then a physical therapy procedure in which emphasis is given to bilateral coordination of gait may reduce FOG in these patients. Such a procedure should be evaluated in the future.

Gait Asymmetry and Other Bilateral Motor Features in Parkinson’s Disease

The clinical motor symptoms of PD often are asymmetric. In most cases, symptoms first appear on one side, and severity of symptoms may remain uneven throughout the disease progression. Thus, it might be
argued that gait asymmetry is merely an expression of disease symptom asymmetry. Our results clearly show that this is not the case. There is no correlation between gait asymmetry and asymmetry in scores of the UPDRS tests. Therefore, it is suggested that gait asymmetry is not a direct reflection of asymmetry in PD symptoms.

Similarly, the findings that group differences regarding asymmetry were seen in gait but not in CAPIT and that levels of gait asymmetry were not correlated with levels of CAPIT asymmetry (see Fig 2C) suggest that PD/FOG have asymmetrical performance which is specific to gait rather than systemic asymmetry in motor performance of rhythmic movements. Note, however, that concluding that the deficit is restricted to the legs is premature. Whereas the CAPIT movements are performed by each hand one at a time, gait requires not only rhythmic repetitions of leg muscle activation, but also bilateral coordination of alternating leg activation. Similar coordination is not required by the CAPIT protocol. A more refined experimental paradigm is needed to clarify this point.

Hypotheses on Freezing

One can hypothesize that (1) asymmetrical and uncoordinated activation of the legs during walking are characteristics of the gait of PD/FOG patients, and (2) asymmetric gait can lead to FOG. Once levels of asymmetrical and uncoordinated gait exceed a certain threshold, gait becomes disarrayed to the extent that it is halted (freezing). Although the former part of the hypothesis is supported by the results of this study, the latter assertion warrants further investigation. Nonetheless, there is some evidence in the literature to support both of these hypotheses.

The basal ganglia (BG), the primary area of impairment in PD, have been shown to be involved in the execution of automatic repetitive movements.26–28 The BG are also likely involved in providing phasic cues to the supplementary motor area (SMA) which regulates both the control of gait29,30 and the bimanual coordination of movements.31–33 Furthermore, it was suggested that in PD patients, but not in healthy controls, the SMA is activated asymmetrically during the control of volitional walking.34 Impaired neuronal output from the BG to the SMA may result in uncoordinated bilateral control of gait, which, at a certain level may lead to FOG.

Table 2. Mean Values (±SD) of Gait Parameters across Experimental Groups and Conditions

<table>
<thead>
<tr>
<th>Swing Time</th>
<th>“Off” State</th>
<th>“On” State</th>
<th>Medication Effect</th>
<th>Group X Medication Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PD + FOG</td>
<td>PD − FOG</td>
<td>p</td>
<td>PD + FOG</td>
</tr>
<tr>
<td>SSWT (sec)</td>
<td>0.22 (0.05)</td>
<td>0.305 (0.05)</td>
<td>&lt;0.0001</td>
<td>0.27 (0.06)</td>
</tr>
<tr>
<td>LSWT (sec)</td>
<td>0.26 (0.06)</td>
<td>0.33 (0.05)</td>
<td>0.001</td>
<td>0.31 (0.05)</td>
</tr>
<tr>
<td>SSWCV (%)</td>
<td>19.2 (8.4)</td>
<td>10.9 (4.3)</td>
<td>&lt;0.001</td>
<td>17.6 (8.6)</td>
</tr>
<tr>
<td>LSWCV (%)</td>
<td>16.4 (6.9)</td>
<td>9.2 (5.3)</td>
<td>0.008</td>
<td>13.3 (9.8)</td>
</tr>
</tbody>
</table>

SD = standard deviation; PD = Parkinson’s disease; FOG = freezing of gait; SSWT = short swing time; LSWT = long swing time SSWCV, short swing CV; LSWCV = long swing CV.

Fig 3. Correlation between rhythmicity of one leg and rhythmicity of the other leg. (A) Swing time variability of the right foot (RSWCV) is plotted against swing time variability of the left foot (LSWCV) in PD−FOG (open squares) during “off” state. There was a statistically significant correlation between the two variables (Spearman’s ρ = 0.682, p = 0.021). (B) Same variables as in A are plotted for PD+FOG (filled squares) patients during the “off” state. No significant correlation was found (Spearman’s ρ = 0.159, p = 0.502). A test for equal correlation (linear) was performed for the data shown in A and B. The two correlations in A and B are significantly different (p < 0.0001).
Support for this idea can be found in the pedaling studies of Abe and colleagues. An abnormal coordination pattern between the legs, including asymmetric force amplitudes, dysrhythmicity in cycling movements, and abnormal cycling phase of one leg with respect to the other, was prevalent among PD patients with freezing. Addressing the findings of that study, Asai and colleagues showed that incorporating asymmetry into a coupled oscillator model simulating the control mechanism of interlimb coordination results in the reproduction of uncoordinated limb movements similar to those described by Abe and colleagues. Both these studies suggest that there is not only an association between asymmetry, variability, and FOG, but also a cause and effect relationship.

Asymmetries reported in this study were seen during open runway gait, in between freezing episodes. Earlier it was reported that many of the freezing episodes occur during turning and during initiation of gait. We argue that these facts support our hypotheses. The load on a system, which is already impaired in bilateral coordination of gait, is increased during turns, compared with open runway walking. During usual walking, the motor commands to each of the legs are rather similar, but during turning the commands are a priori different (eg, one leg is primarily pivotal). The bilateral coordination which is required for turns, then, is more complicated, and more likely to fail if basic bilateral coordination is impaired. Along these lines, initiation of gait can be considered as the “ultimate” asymmetrical walking task because only one leg is required to start walking while the other leg provides antigravitational support. Nonetheless, additional studies are required to further explore the causal pathway of FOG.

This work was supported by grants from the NIH (National Institute on Aging, AG-14100, AG-08812; National Center for Research Resources, RR-13622; National Institute of Child Health and Human Development, HD-39838; J.M.H.).

We thank all the patients who contributed their time and effort to participate in this study. We also thank Drs J. D. Schaafisma and A. L. Bartels for their invaluable assistance.

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