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Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease

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To assess the effect of levodopa on distinct freezing of gait (FOG) subtypes in patients with 'off' FOG. Nineteen patients (12 men, mean age 62.0 ± 8.4 years) with Parkinson's disease and clinically significant FOG during 'off' states were videotaped whilst walking 130 m during 'off' and 'on' states. Three independent observers characterized the type, duration, and clinical manifestations and quantified FOG by analyzing the videotapes. Their combined mean scores were used for statistical analysis. The intra-class correlation coefficient assessed inter-observer reliability. Wilcoxon and Friedman tests evaluated differences in mean frequencies of FOG characteristics. During 'off' states, FOG was elicited by turns (63%), starts (23%), walking through narrow spaces (12%) and reaching destinations (9%). These respective values were only 14, 4, 2 and 1% during 'on' states ($P < 0.011$). Moving forward with very small steps and leg trembling in place were the most common manifestations of FOG; total akinesia was rare. Most FOG episodes took < 10 s and tended to be shorter during 'on' states. Levodopa significantly decreased FOG frequency ($P < 0.0001$) and the number of episodes with akinesia ($P < 0.001$). Distinction amongst FOG subtypes enables evaluation of distinctive therapeutic response. Levodopa helps in reducing the frequency and duration of 'off'-related FOG.

Introduction

About one-third of patients with Parkinson's disease (PD) experience sudden and transient disturbances in the performance of motor behavior, also known as the 'freezing phenomenon' (Giladi *et al*., 1992; Denny and Behari, 1999). Freezing of gait (FOG) can be very disabling, impairing mobility and restricting independence. Typically, FOG is a transient episode, lasting < 1 min, in which gait is halted and the subject complains that his feet are glued to the ground. When the patient overcomes the block, walking can be performed relatively smoothly.

Whilst others have reported the most common form of FOG to be start hesitation followed in frequency by turning hesitation (Giladi *et al*., 1992; Fahn, 1995; Lamberti *et al*., 1997; Denny and Behari, 1999) the findings of our recent study showed turning hesitation to be the most frequent type of FOG in PD patients (Giladi *et al*., 2002). FOG can also be experienced in narrow or tight quarters such as a doorway, whilst adjusting one's steps when reaching a destination, and in stressful situations such as when the telephone or the doorbell rings or when the elevator door opens. As the disease progresses, FOG can appear spontaneously even in an open runway space, thus highlighting the unpredictable aspect of this phenomenon.

The study of FOG has been hampered by a number of obstacles. Because FOG tends not to occur during office visits to the physician or in the gait laboratory, most FOG assessments have had to rely on patients' answers to subjective historical questionnaires (Narabayashi, 1985; Narabayashi and Nakamura, 1985b; Giladi *et al*., 1992, 1997, 2000, 2001c; Lamberti *et al*., 1997). Our recent FOG questionnaire was the first validated tool designed to assess FOG but it, too, is a subjective assessment (Giladi *et al*., 2000). In addition, attempts to quantify FOG have always involved lumping different types of FOG together into one group or one symptom. If, however, it emerges that different types of FOG have different pathophysiologic origins, there will be a need to classify FOG into distinctive subgroups. It follows that an exact clinical characterization of the different types of FOG and an objective assessment of each of them should help to improve the current understanding of FOG and suggest avenues for future research.

The current study is the first attempt to objectively quantify FOG by using a structured video assessment evaluated by three independent expert observers. We subdivided FOG not only according to the motor state

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during which it occurred, but also according to the motion of the legs that had been observed during the event as well as the duration of each episode. We used the results of this objective assessment for answering the question of whether levodopa treatment improves 'off' FOG: the pertinence of this question lies in the fact that FOG can occur at 'off' and 'on' unrelated to the motor state, thus making the relationship between its occurrence and the administration of the drug unclear.

Methods

Clinical evaluation

We selected 19 patients with PD who were on levodopa treatment at the Movement Disorders Unit of the Department of Neurology in the Tel Aviv Sourasky Medical Center. PD was defined according to the Diagnostic Criteria for PD (Gelb *et al.*, 1999). All the subjects experienced marked FOG on examination at their early morning 'off' state. In order to study a homogeneous group of patients with classical PD, we excluded patients who reported that they walk much better before the first morning dose of levodopa and freeze shortly after turning to the 'on' state (dopa-induced 'on' freezing). Patients who were unable to complete a walking task during an 'off' state were excluded as well. The study was approved by the local human studies/Helsinki committee. All subjects provided informed consent.

Patients were examined during 'off' states, at least 12 h after their last anti-parkinsonian medication, and during 'on' states, approximately 1 h after they took their regular morning dose of levodopa. If, as a result of the unusual situation of being examined early in the morning without having taken their regular morning medication, patients were in an 'on' state or only partially 'off', we waited until a full 'off' state had developed before the initial assessment was performed.

The assessment during the 'off' state included part three (motor examination) of the UPDRS (Fahn *et al.*, 1987) and assessment of the Hoehn and Yahr stage (Hoehn and Yahr, 1967). The patients were also asked to leave the examination room, walk through the corridor, and enter the gait laboratory (25 m). In the gait laboratory, they got up from a chair, walked 20 m, turned 360° to the right and 540° to the left, and walked back the same way, returning to the chair. At the 10-m mark, patients walked in between two chairs, 50 cm apart to simulate a narrow path. After completing two laps or 80 m, they walked back the same way to the examination room. For three patients who were in a severe 'off' state but still able to walk the 80 m, we used a wheelchair to bring them to and from the gait lab. The entire walking task (130 m) was videotaped and used for evaluation. All patients watched one demonstration of the walking task and were then instructed to walk as soon as possible after being given the signal to walk. They were asked to try to overcome any hesitation episode as quickly as possible should one have occurred.

After the 'off' assessment, the patient took the regular morning dose of levodopa and we waited until he/she reported to have reached a characteristically good 'on' state. Full UPDRS and the walking task were performed and videotaped a second time.

Video assessment

Three independent observers, each with extensive experience in FOG assessment, analyzed the videotapes. The recorded FOG episodes were characterized with respect to the situation in which they occurred (type), the motion of the legs during the block (manifestation), and the duration (in seconds) of each episode.

A FOG episode was defined by the patient's not responding within 1 s to the instruction to walk or if it appeared as if he/she were trying unsuccessfully to initiate or continue locomotion. A transient and clinically significant break in locomotion for no apparent reason was also considered to be FOG. In order to avoid any deliberate concentration of the patients on their gait during this assessment, we did not ask them to report subjective feelings of FOG or to count the episodes.

Types of FOG

We distinguished five types of FOG according to the subgroup classification of Fahn, 1995: (i) start hesitation, when freezing was detected as the patient initiated walking; (ii) turn hesitation, when the feet appeared to become stuck whilst making a turn; (iii) apparent hesitation in tight quarters (i.e., when FOG was noted when the patient passed through a narrow space); (iv) destination-hesitation, when the feet appeared to freeze as the patient approached a target (the final 2 m of the task), and (v) open space hesitation (i.e., when the patient seemed to experience a spontaneous freezing episode whilst walking in an open space without an apparent provoking factor such as doorway). Freezing episodes were considered destination hesitations and not open space hesitations when the feet became stuck < 2 m before a narrow passageway, before the full turns at the 20-m mark, and before reaching the chair at the end of each lap. The number of occurrences of each type of FOG episode was counted and recorded for each patient.

Because the occurrence of FOG episodes depends on the execution of eliciting actions, such as initiating walking or turning, we calculated percentages to reflect the proportional frequency of these types of FOG, e.g., the percentage of turning hesitations out of all the turns in the given task. It was not possible to calculate the frequency percentage of hesitations in an open space because there were no specific eliciting actions: instead, we looked at the number of such episodes each patient experienced throughout the whole examination.

Manifestations: leg motions associated with FOG episodes

Freezing of gait episodes were also subdivided according to the associated leg motion observed on the video according to the classification of Thompson and Marsden (1995). The three manifestations of FOG that were distinguished included: (i) FOG associated with very small shuffling steps and with minimal forward movement (shuffling with small steps), (ii) FOG with some leg trembling but no effective forward motion (trembling in place), and (iii) complete akinesia, i.e., no observable motion of the legs. The leg motion of each episode was assessed and recorded.

Duration

We divided the duration of FOG episodes using the same cut-off points as in the FOG questionnaire (Giladi *et al*., 2000): 0–2, 3–10, 11–30 s and more than 30 s. Because of the difficulty in determining when hesitation starts or ends during a turn in the absence of any clearly observable motion before or after hesitation, we could not estimate the duration of a turning hesitation episode.

The three observers were instructed to time the initiation of start hesitation from 1 s after the patient was instructed to initiate walking but had not yet performed any effective step forward. Hesitation in an open space or in tight quarters was timed from the time a block or hesitation had occurred during locomotion. The end of an episode was defined as the time when an effective step had been performed with a relatively normal length and swing; the step also had to be followed by continuous normal locomotion. At least two normal steps were required in order to score and time the duration of a freezing episode. The video segment of each episode had to be played back several times frequently in order to time its duration with precision.

Statistical analysis

All statistical analyses were performed after we evaluated the agreement between the three observers. The inter-observer reliability was evaluated using the intra-class correlation coefficient (Shrout and Fleiss, 1979). We used the following classification (Armitage and Berry, 1994) to indicate the power of the correlation coefficients: $R = 0.01$–0.2: negligible, $R = 0.2$–0.4: weak, $R = 0.4$–0.7: moderate, and $R = 0.7$–0.9: strong. The Friedman non-parametric test was used to examine differences between the three observers.

After combining the results of the video assessment of the three observers, we evaluated the different characteristics of a FOG episode. The mean of the three independent observations was used as a representative measure. The Wilcoxon signed rank test, a non-parametric test analogous to a paired *t*-test, was used to compare the percentages of start hesitation, turn hesitation, hesitation in tight quarters, and hesitation upon reaching a destination; each one was compared with one another as well as between the 'off' and 'on' states.

We used the Friedman non-parametric test to compare the four periods of duration during both 'off' and 'on' states. Fisher's exact test was used to assess the change in distribution in 'on' states. Wilcoxon non-parametric tests were applied to compare the periods of duration between the 'off' and 'on' states. The different motor manifestations were analyzed in the same way as were the different divisions of duration. Differences with *P*-values < 0.05 were considered significant. We used Bonferrini corrected values to preserve the 0.05 level and control the experiment-wise error rate.

Results

The pertinent characteristics of the study patients are summarized in Table 1. In general, there was a high level of agreement ($R > 0.7$) between the three observers, although there was little agreement for several variables. The scores for turn hesitation during 'off' and 'on' states and the scores for FOG episodes during

Table 1 Characterization of the study population: 19 patients with Parkinson's disease and 'off' state freezing of gait (FOG)

Gender	Twelve men/seven women
Age (years)	63 (50–78)
Hoehn and Yahr stage	
'Off' state	3 (2.5–4)
'On' state	3 (2–4)
Duration of symptoms (years)	12 (5–18)
UPDRS total score ('on' state)	27 (9–49)
UPDRS motor score (part III)	
'Off' state	23 (13–43)
'On' state	10 (3–23)
Daily dose of levodopa	730 mg (375–1675)

Results are given as mean (range).

'off' and 'on' states differed significantly ($P < 0.05$) amongst the observers. However, the correlation between the observers was strong ($R > 0.8$) indicating that the differences were consistent.

Only the scores on frequency of the 'trembling in place' type of turn hesitation during 'off' states differed significantly ($P < 0.0001$) and showed a moderate correlation ($R = 0.48$). The intra-class correlation for scoring the type of FOG was strong ($R = 0.76$). The intra-class correlation was moderate for duration and the relation to leg motion of the FOG episodes, $R = 0.63$ and 0.64, respectively. Because of the overall strong correlation between the scores of the observers ($R > 0.7$), we took the average in order to combine the scores of the three observers.

Types of freezing of gait

All 19 patients experienced FOG during 'off' states according to the study inclusion criterion. FOG was also observed during the 'on' state in eight patients. The frequencies of the five types of FOG are presented in Table 2.

Figure 1 shows the frequency of all types of FOG amongst 19 PD patients with freezing during 'off' states. Overall, turn hesitations, start hesitations, hesitations whilst passing through a narrow space, and destination hesitations were significantly less common during 'on' states compared with 'off' states.

In the 'off' states, the frequency of turn hesitations was significantly higher than the frequencies of hesitations in tight quarters, start hesitations and destination hesitations ($P < 0.0001$, $P = 0.003$ and $P < 0.0001$, respectively). However, in the 'on' states, the frequency of each type of freezing did not differ significantly from the other types. This may be due to a lack of power because the total number of episodes in the 'on' state was small. Still, it could be said that there was a tendency toward a higher prevalence of turn hesitations during 'on' states ($P < 0.125$).

FOG in relation to leg motion

Sixteen patients (84%) in the 'off' state and six (75%) in the 'on' state demonstrated the 'small steps' type of FOG at least once. Trembling in place was manifested by 16 patients (84%) in the 'off' state and by five (63%) in the 'on' state at least once. Seven patients (37%) exhibited complete akinesia but only during the 'off' state. According to one observer, one patient (13%)

Table 2 Prevalence of types of freezing of gait (FOG) presented as frequency amongst 19 patients with PD at 'off' and 'on' states

Type of hesitation	No. of patients with FOG at 'off' state (%)	Mean number of episodes	No. of patients with FOG at 'on' state (%)	Mean number of episodes
Turn	18 (95)	4.4	6 (32)	4.4
Start	11 (58)	2.2	1 (5)	1.7
Tight quarters	7 (37)	1.5	2 (11)	1.3
Upon reaching destination	7 (37)	2.0	1 (5)	1.0
In an open runway	6 (32)	2.5	0	0

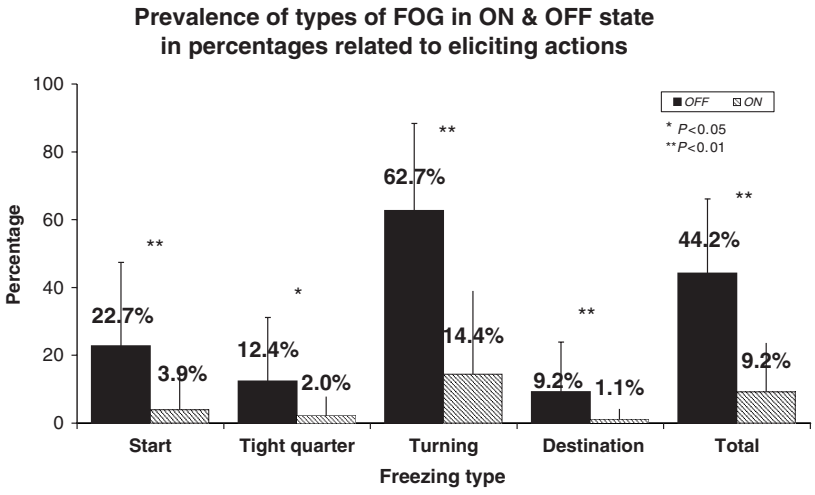

Figure 1 Prevalence of freezing episodes as a function of different types of eliciting events. The black bars represent the percentage ± SD of the freezing of gait (FOG) types at the 'off' state and the light bars represent the percentage ± SD of the FOG types at the 'on' state. FOG was significantly less common ($P < 0.05$) for all tasks as well as for the entire protocol during the 'on' state.

experienced akinesia during one freezing episode in the 'on' state. The frequency of the different manifestations was calculated for each patient (Fig. 2).

There was a significant reduction in the frequency of the observed episodes in the 'on' state compared with the 'off' state for all three manifestations ($P < 0.001$). Of note, the distribution of all the manifestations was also significantly different during the 'on' and 'off' states (i.e., there was a significant interaction between medication state and manifestations, $P < 0.001$). Small step FOG was most common during the 'off' state. The second most common FOG was trembling in place, whilst akinesia was least prevalent. However, the prevalence of small steps and trembling in place was comparable in the 'on' state whilst akinesia had almost vanished. More generally, FOG in 'on' states was associated with more motion, as can be seen by the relatively higher frequencies of the 'shuffling forward' and 'trembling in place' types of FOG. Although seven patients experienced the akinesia type of FOG in the 'off' state, akinetic FOG was generally infrequent, occurring in approximately 10% of all episodes.

Duration of FOG

Freezing of gait episodes are stratified by duration in Fig. 3. Most episodes lasted < 10 s in both the 'off' and 'on' states. Episodes longer than 30 s were very rare and the longest FOG did not last more than 10 s in the 'on' state. We observed a tendency for shorter FOG episodes during 'on' states compared with 'off' states ($P = 0.143$). The difference amongst the frequencies of the four intervals during 'off' states and 'on' were all significant ($P < 0.0001$ and $P = 0.0001$, respectively).

Discussion

This study was designed to distinguish amongst FOG subtypes in order to enable the evaluation of the therapeutic response of levodopa to each of them in

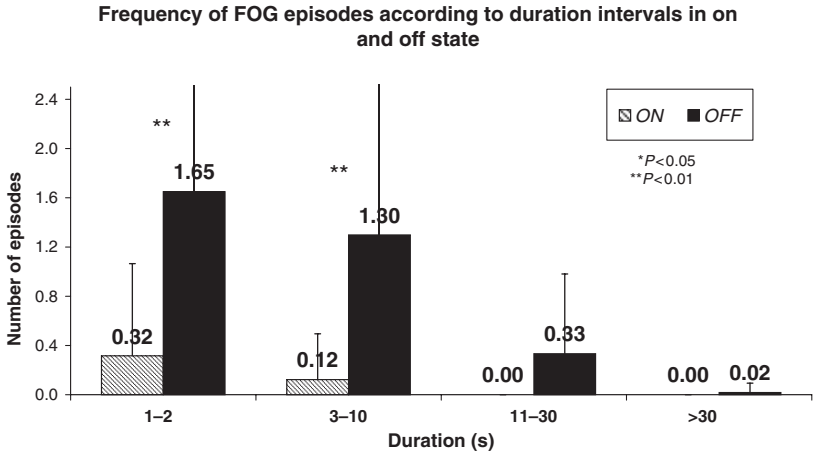

Figure 2 Duration of freezing of gait (FOG) episodes as a function of episode duration as classified in the FOG questionnaire. None of the episodes lasted longer than 10 s at the 'on' state. In general, FOG was significantly shorter in the 'on' state.

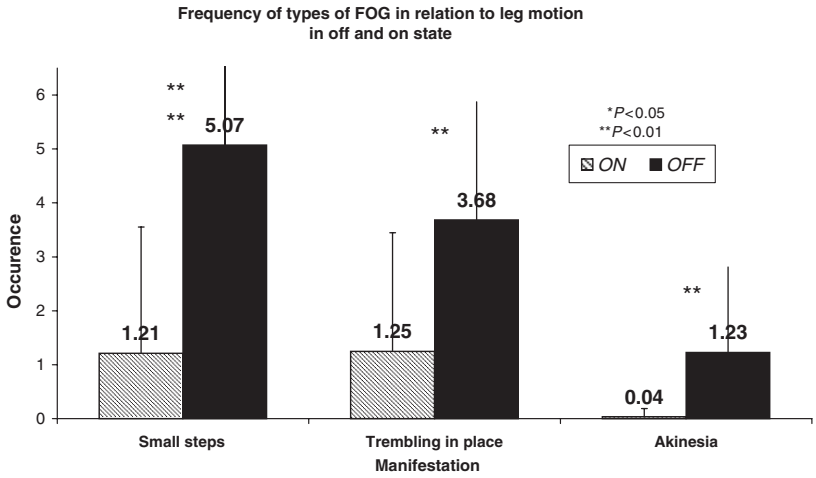

Figure 3 Frequency of the three subgroups of FOG characterized by the leg movements associated with the freezing episode. No leg movements – akinesia was seen during the 'on' state. FOG episodes with small, ineffective, shuffling and trembling of legs were significantly less common in the 'on' state

isolation. We found that turning is a very effective provocative task to induce an 'off' state FOG and that total akinesia was rare even during 'off' states, compared with moving forward with very small steps (shuffling) and leg trembling in place. Most FOG episodes took < 10 s and tended to be shorter during 'on' states. Levodopa significantly decreased the frequency of 'off' state FOG episodes ($P < 0.0001$) as well as the number of akinetic episodes ($P < 0.001$).

Despite its importance to daily function and its high frequency, very little has been done in order to characterize FOG according to the various specific forms in which it is expressed. The analysis of FOG by three independent observers based on videotapes during 'off' and 'on' states enabled us to quantify FOG for the first time in terms of type, motor manifestation, and duration of each episode. Such an objective assessment also gave us the opportunity to quantify the response of each subgroup of FOG to levodopa treatment.

Types of freezing

Turn hesitation was the most common type of FOG in the 'off' and 'on' states in this study. This is consistent with our previous preliminary report (Giladi *et al.*, 2002). We noted that many patients only experienced FOG in the full turns (360–540°) and not in the partial turns (180°) that were performed in a continuation of motion whilst preparing to sit on a chair at the completion of the task. We think that the disagreement of our finding about the most frequent FOG with those of previous reports (Giladi *et al.*, 1992, 2002; Fahn, 1995; Lamberti *et al.*, 1997; Denny and Behari, 1999) is the result of our having included a large proportion of turns in our protocol. We speculate that patients may not report their turn hesitations because full turns are not common motions in everyday life. However, from a functional point of view, turn hesitations might have clinical importance because patients are less stable and the risk of falling might be higher whilst they are turning. Furthermore, turns seem to be a strong provocative factor for FOG and a good tool for FOG assessment.

Freezing of gait subtypes that appear to be somewhat similar in performance might have a very different pathophysiology. In order to assess this possibility in the future, precise characterization is essential as is agreement about the subtypes of FOG.

Manifestations of freezing

In this study, 'small steps' and 'trembling in place' appeared to be far more common than 'akinesia'. This suggests that FOG is not a total block without movement. For this reason, 'freezing' may not be the appropriate term for this phenomenon. The reason for akinetic FOG is still unclear. One possibility is true inability to execute movement, despite a strong desire. A probable explanation is that the patient is unable to generate the inner drive to initiate movement. The first possibility is associated with a motor block whilst the second may be more appropriately termed a 'mental block'. It remains to be seen if the mechanisms of akinetic freezing and freezing with movement are different.

This phenomenological study supports previous physiologic lines of research that demonstrated tremor-like movements of the legs during some FOG episodes. The origin of this tremor-like motion in the legs is not clear. If it is, indeed, tremor, it should be considered an action tremor. Considering its association with specific tasks, its appearance mainly during actions, its typical 4–6 Hz frequency (Ueno *et al.*, 1993), and the co-activation of antagonist muscles (Andrews, 1973), we suggest that this is an atypical form of action legs dystonia or dystonic tremor (Giladi *et al.*, 2001a).

Freezing as a paroxysmal event

Highlighting the fact that FOG is a transient entity, most episodes evaluated in the current study lasted for 1–2 s and almost all episodes lasted < 10 s. Moreover, FOG occurred in $< 50\%$ of all potential episodes.

Response to levodopa

All types of FOG in this study improved significantly with levodopa treatment. Such an effect had been the clinical impression of many but was also questioned by others who, in contrast, observed an increase in FOG frequency in association with levodopa treatment (Ambani and Van Woert, 1973; Giladi *et al.*, 1992). This current study, for the first time, demonstrated the positive effect of levodopa on FOG using objective measures. Levodopa treatment clearly decreased the frequency and the akinetic type of FOG, with a tendency for shorter FOG episodes. However, this observation should take into account that we examined only patients with 'off' state FOG and excluded patients with 'on' state FOG. One can conclude from our findings that the type of FOG, which appears predominantly during 'off' states, improves with levodopa treatment. This is in contrast to the 'on' state FOG, which is worsened by levodopa. Based on this difference, we hypothesize that the physiology of 'off' state FOG is different from the 'on' state FOG.

The clinical appearance of each FOG subtype did not change between the 'off' and the 'on' state despite being less frequent and more dynamic during 'on' with a trend

toward a shorter duration. These results may suggest that levodopa treatment only increased the threshold for FOG to occur, but did not change the basic pathophysiology. This is in contrast to a recent attempt to change for basic pathophysiology by injecting botulinum toxin to calf muscles (Giladi *et al*., 2001a).

Interestingly, drugs from the dopamine agonist (DA) group had different effects on FOG. Recent studies have suggested that DA may increase FOG frequency, especially in the early stages of PD (Ahlskog *et al*., 1992; Parkinson Study Group, 2000; Rascol *et al*., 2000) as well as in later more advanced stages (Wiener *et al*., 1993; Giladi *et al*., 2001c). In contrast, apomorphine is known to improve FOG (Corboy *et al*., 1995). This fundamental difference between levodopa and DA treatment in regard to the effect on FOG may suggest that the specific dopamine receptor subtype (D1) is playing an important role in the effectiveness of levodopa on FOG. It is known that DAs, such as ropinirole, pramipexole and pergolide, have high affinity for D2 receptors in contrast to apomorphine that has high affinity to D1 and D2 receptors (Arnt *et al*., 1988). Selegiline was recently reported to prevent FOG very effectively (Giladi *et al*., 2001b; Shoulson *et al*., 2002). Considering the fact that selegiline increases monoamine metabolites (dopamine and norepinephrine), it is possible that the receptor activation profile of endogenous dopamine or exogenous apomorphine is more efficacious than most DA drugs, increasing the threshold for paroxysmal disturbances of electrical activity at the level of the basal ganglia.

Limitations of this study

We believe this to be the first time that FOG was analyzed objectively and systematically by means of assessment of video recordings. Whilst the results extend our knowledge about FOG, it should be remembered that FOG has a significant subjective component. Specifically, the affected individual 'feels' that the feet are glued to the floor. We did not ask the patients if they felt having experienced a freezing episode, so we might have missed very brief or subtle episodes. Furthermore, our strict division between either 'off' and 'on' states did not take into account the whole spectrum between the two. As a result, we could not relate the severity of FOG to the severity of 'off' states or the quality of 'on' states.

It is possible that the improvement in walking during 'on' states could be a result of practice. However, there was not only a decrease in the frequency of the episodes, but also a change in the duration of FOG and a significant improvement of part III of the UPDRS ($P < 0.001$), which is unlikely to be achieved by practice alone. Finally, the protocol was overloaded with turns. Although not representative of real-life behavior, this feature is scientifically important because it is a strong provocative action for freezing.

The high frequency and degree of disability caused by FOG motivates further research and the development of new treatments. An important first step in this direction is the creation of a single, precise and accepted nomenclature to improve communication between researchers. We believe that the present study sheds some light on clinical and phenomenological issues that are the basis of freezing research. The clear response of each of the subtypes we delineated to levodopa is an encouraging finding that gives hope for the development of an effective treatment in the near future.

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