J Neurol
DOI 10.1007/s00415-012-6585-4

ORIGINAL COMMUNICATION

Asymmetry and freezing of gait in parkinsonian patients

Giuseppe Frazzitta · Gianni Pezzoli · Gabriella Bertotti · Roberto Maestri

Received: 24 February 2012 / Revised: 16 April 2012 / Accepted: 11 June 2012

Abstract It has been hypothesized that freezing of gait (FOG) in parkinsonian patients (PD) might be triggered by a breakdown in the normal symmetry of gait. In this study, we evaluated the relationship between asymmetry of gait and FOG and the effects of intensive treadmill treatment on asymmetry. We studied 30 patients with (FOG+) and 30 without (FOG−) freezing in "on" stage. Patients underwent a 4-week rehabilitation treatment using a treadmill with auditory and visual cues and were evaluated at enrolment and at the end of rehabilitation. Outcome measures were gait speed, stride length, asymmetry of gait, Six-minute walking test (6MWT), Unified Parkinson's Disease Rating Scale (UPDRS) II–III, Berg Balance Scale, Timed Up and Go Test, comfortable-fast gait speeds, freezing of gait questionnaire (FOGQ). At enrolment, no differences in gait parameters were observed between the two groups, which differed only in UPDRS_II and BBS. Both FOG+ and FOG− patients spent more time on the left foot (time on left/time on right foot 1.37, $p = 0.002$, 1.18, $p = 0.016$, respectively). Rehabilitation determined a homogeneous improvement in both groups of patients for all variables except UPDRS_II and balance, for which a better improvement was observed in FOG+ patients. The improvement in FOGQ in FOG+ patients was significantly correlated to the improvement in asymmetry of gait (Spearman $R = 0.46$, $p = 0.013$). Our data support a direct involvement of the asymmetry of gait in the development of FOG in PD. Treadmill training is effective in improving gait and balance in PD FOG+ patients and this might be related to a reduction of asymmetric gait.

Keywords Parkinson's disease · Freezing of gait · Asymmetry of gait · Rehabilitation

Introduction

Impairment of gait is an important symptom in parkinsonian patients (PD). The alteration of gait parameters manifests from the beginning of the disease and generally worsens over time [1]. Gait disturbances may be classified as continuous (reduction of stride length and gait speed, increased double support time, stride to stride variability and left–right asymmetry) and episodic (festination and freezing). Both types of gait disturbances are strongly disabling because they impair mobility and worsen the quality of life of patients [2]. Freezing of gait (FOG), which can often lead to falls in PD, is often triggered by environmental constraints requiring a change in gait direction, pattern, or speed, such as getting over an obstacle, walking in confined spaces, or reaching a destination.

FOG is very difficult to treat pharmacologically since, while patients with FOG in "off" state benefit from an increase in levodopa dosage, patients with FOG in "on" state commonly show only a partial response to drugs [3, 4].

G. Frazzitta (✉) · G. Bertotti
Department of Neurorehabilitation, Scientific Institute of Montescano, S. Maugeri Foundation IRCCS, Via per Montescano, 27040 Montescano, PV, Italy
e-mail: giuseppe.frazzitta@fsm.it

G. Pezzoli
Parkinson Institute, Istituti Clinici di Perfezionamento, Milan, Italy

R. Maestri
Department of Biomedical Engineering, Scientific Institute of Montescano, S. Maugeri Foundation IRCCS, Montescano, Italy

Published online: 01 July 2012

The use of a treadmill has proven useful in the rehabilitation of gait disorders in PD and in particular the use of treadmill training in association with auditory or visual cues is effective in improving FOG in PD [5, 6].

The patho-physiological mechanisms underlying FOG are still poorly understood. The symptoms of Parkinson's disease generally show an asymmetric onset and progression. It has recently been hypothesized that this may lead to a degree of asymmetric motor function, and that FOG is triggered by a breakdown in the bilateral co-ordination underlying the normal timing of gait.

This study was devised to evaluate the relationship between asymmetry of gait and FOG in PD and the effects of intensive treadmill treatment on asymmetry.

Methods

Study protocol

We screened patients with a diagnosis of "clinically probable" idiopathic Parkinson's disease according to Gelb et al. [7], consecutively admitted to our hospital for rehabilitation treatment. Inclusion criteria were ability to walk without any physical assistance, visual and hearing capacity sufficient to perceive the cues, no cognitive impairment (mini-mental state examination score >26) [8], stable pharmacological treatment in the last 8 weeks, Hoehn–Yahr stage 3. Patients were assigned to two groups according to the presence or not of FOG in the "on" period when performing a rapid full turn and normal gait trajectory [9].

Subjects were excluded if they had neurological conditions other than idiopathic Parkinson's disease, postural hypotension, cardiovascular disorders, musculoskeletal disorders, or vestibular dysfunction limiting locomotion or balance.

Screening was stopped when 30 patients with gait disturbance but without FOG in "on" stage (group 1, FOG−) and 30 patients with FOG in "on" stage (group 2, FOG+) were enrolled. All patients underwent the same rehabilitation protocol for gait disturbances and FOG using treadmill training associated with auditory and visual cues. A motorized medical treadmill (Locomotor Training-Biodex, USA) was used. The device is endowed with four strain gages under the belt, sensitive to the bending of the belt itself caused by the weight applied by the patient walking. These gages are connected to software that allows to reproduce the shapes of feet on the screen and to compute several gait parameters.

All patients were familiarized with the motorized treadmill before performing the evaluation at the start of the rehabilitation program.

Subjects received treadmill training for 30 min every day for 5 days/week, for 4 weeks (20 sessions in total). The patients were observed during training by a physiatrist.

Maximum tolerated walking speed was determined before the training session. This speed was reduced (−40 %) and used for a 2-day warm-up period. After that, the belt speed was increased every 3 days by 0.05 stride cycles/s. During the training, a visual cue and an auditory cue were used. The visual cue was a target displayed on a screen that the patient had to reach with the stride. The shapes of right and left foot were shown alternatively on the screen. When the patient's stride fell within the set standard deviation (SD), the footfalls were synchronized with the target shapes and "well done" appeared on the screen. When the stride fell outside the SD, the footfalls and target shapes were out of synchronization and the patient was informed, on the screen, of which footfall was outside of the SD and prompted to take a longer or shorter step with the respective foot. The auditory cue consisted of musical beats synchronized with the visual cues with a frequency of 0.5 c/s.

The same neurologist specialized in movement disorders and blinded to the study design examined the patients in the morning, 1 h after they had taken levodopa during the "on" stage, at baseline, and at the end of the rehabilitation treatment.

Due to the advanced stage of the disease, all patients developed bilateral symptoms but on the basis of anamnestic data and symptoms, each patient could be classified as being mostly affected on the right or on the left side. This information was used to investigate whether a dependency of the asymmetry from the most affected side was present.

The rating scales used for the clinical evaluation were the UPDRS II and III [10], the Freezing of Gait Questionnaire (FOGQ) [11], Six-minute walking test (6MWT), the TUG, the Comfortable (CGS) and Fast gait speeds (FGS) [12, 13], and the Berg Balance Scale (BBS) [14].

Among gait parameters automatically computed by the software of the treadmill, we considered gait speed, stride length, and time on each foot. We computed the ratio between the time spent on the left and on the right foot during gait, as an index of gait asymmetry (gait_asym).

The study was approved by the local Scientific Committee and Institutional Review Board (Fondazione S. Maugeri, IRCCS, Istituto Scientifico di Montescano). Written informed consent was obtained from all patients before participation.

Statistical analysis

Shapiro–Wilk statistic was used to test the normality of the distribution of all variables.

Within-group comparisons were carried out by paired t test or by Wilcoxon's matched-pairs test in case of violation of the normality assumption. Between-group comparisons were carried out by unpaired t test or by Mann–Whitney U test, if appropriate. Descriptive statistics are given as mean ± SD.

The effect of the rehabilitation on each outcome variable in relation to FOG was assessed by a two-factor analysis of variance: group of patients (FOG+ and FOG−) and time (end of treatment versus baseline), with repeated measures in the time factor.

The strength of the association between asymmetry, FOGQ, and parameters related to gait was assessed by the Spearman R coefficient. A p value <0.05 was considered statistically significant. All analyses were carried out using the SAS/STAT statistical package, release 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Table 1 reports all considered variables at admission in FOG− (group 1) and FOG+ patients (group 2). On the overall population, the time spent on the left foot during gait was higher than that spent on the right one (gait_asym = 1.28, $p = 0.0001$). This asymmetry was observed also considering FOG− (gait_asym = 1.18, $p = 0.0164$) and FOG+ patients (gait_asym = 1.37, $p = 0.002$). Even though there was a tendency towards a higher level of asymmetry in FOG+ patients than in FOG− patients, this difference was not statistically significant ($p = 0.13$).

Considering the subgroup of patients mostly affected on the right side, again this difference was pronounced (gait_asym = 1.36, $p = 0.0001$), while in the subgroup of patients mostly affected on the left side, the trend was confirmed, but the difference did not reach statistical significance (gait_asym = 1.14, $p = 0.16$).

No statistically significant differences in variables related to gait (gait speed, stride length, percentage time on each foot, and 6MWT) were observed between the two groups of patients, even though a tendency towards better performances was observed in FOG− patients. As far as the other scales are concerned, FOG− patients showed better values in UPDRS II and BBS scales ($p = 0.001$ and $p = 0.010$, respectively) while TUG, CGS, and FGS were not different.

Considering the effect of rehabilitation (Table 2), an improvement was observed in all variables in both groups of patients as assessed by the analysis of variance showing a time effect p value <0.0001 for all variables except gait_speed ($p = 0.007$) and gait_asym ($p = 0.0002$). The improvement was homogeneous in both groups of patients for all variables except UPDRS II and BBS scores, for which a significant time-treatment interaction was observed ($p = 0.0059$ and $p = 0.0213$, respectively), indicating that the changes of these scores due to treatment were different in FOG+ and FOG− patients with a better improvement in FOG+ patients.

In FOG+ patients, we found a significant correlation between asymmetry of gait and FOGQ (Spearman $R = 0.45$, $p = 0.015$ at enrolment), between improvements in gait asymmetry and improvements in right stride length ($R = 0.44$, $p = 0.014$) and between improvements in gait asymmetry and improvement in FOGQ ($R = 0.46$, $p = 0.013$).

Discussion

FOG is a disabling phenomenon commonly observed in patients with advanced Parkinson's disease. Its response to

Table 1 Values at admission in patients without (FOG−) and with (FOG+) freezing in the ON state

Variable	FOG−	FOG+	p value
Age (years)	70.8 ± 8.2	69.6 ± 9.1	0.589
L-DOPA (mg/day)	750 ± 277	771 ± 247	0.673
UPDRS_II	13.47 ± 4.4	18.40 ± 5.9	0.001
UPDRS_III	19.27 ± 4.4	22.03 ± 6.7	0.109
FOGQ	4.3 ± 1.1[a]	13.53 ± 2.6	
SixMWT (m)	322.13 ± 89.5	280.88 ± 92.3	0.084
Gait_speed (m/s)	0.89 ± 0.2	0.78 ± 0.3	0.084
Stride_length_dx (m)	0.38 ± 0.1	0.36 ± 0.1	0.634
Stride_length_sx (m)	0.40 ± 0.1	0.41 ± 0.1	0.522
Gait_asym	1.18 ± 0.4	1.37 ± 0.6	0.131
BBS	46.9 ± 10.4	43.3 ± 8.4	0.010
TUG (s)	10.3 ± 3.1	11.7 ± 3.8	0.208
CGS (m/s)	1.01 ± 0.2	0.92 ± 0.3	0.247
FGS (m/s)	1.29 ± 0.3	1.16 ± 0.3	0.097

L-dopa dosage includes dopamine agonists

[a] Values of FOGQ for patients without freezing of gait were obtained considering only the first two items, pertaining to mobility

Table 2 Changes (delta) between discharge and admission in all considered variables in patients without (FOG−) and with (FOG+) freezing in the ON state

Variable	FOG−	FOG+	*p*-time	*p*-interaction
UPDRS_II	−4.1	−6.5	<0.0001	0.0059
UPDRS_III	−5.8	−7.2	<0.0001	0.1223
FOGQ	−3.1[a]	−5.5	<0.0001	
SixMWT (m)	87.0	69.9	<0.0001	0.2707
Gait_speed (m/s)	0.2	0.2	0.0069	0.5033
Stride_length_dx (m)	0.1	0.1	<0.0001	0.8743
Stride_length_sx (m)	0.1	0.1	<0.0001	0.4050
Gait_asym	−0.3	−0.2	0.0002	0.1833
BBS	4.8	8.0	<0.0001	0.0213
TUG (s)	−2.3	−2.6	<0.0001	0.4893
CGS (m/s)	0.22	0.18	<0.0001	0.4482
FGS (m/s)	0.20	0.18	<0.0001	0.6853

The *p* values for time effect and for the interaction (time × group) from repeated measures analysis of variance are also reported

[a] Values of FOGQ for patients without freezing of gait were obtained considering only the first two items, pertaining to mobility

pharmacological treatment is highly variable. In particular, patients showing freezing in the “on” state usually do not benefit from an increase in levodopa dosage.

It remains a poorly understood phenomenon and different hypotheses have been proposed to clarify its pathogenesis [15].

In this study, we investigated the relationship between the level of asymmetry of gait and FOG in PD and assessed the effectiveness of a rehabilitation treatment based on treadmill training with auditory and visual cues on gait parameters in FOG+ and FOG− patients, testing the association between improvement of freezing and improvements in the level of asymmetry.

At enrolment, we found no differences between FOG+ and FOG− patients in all parameters related to gait. Interestingly, we observed a significant increase in the time spent on left foot in the overall population. This asymmetry was common to both groups of patients: it was more pronounced in patients mostly affected on the right side, but the trend was confirmed also in patients mostly affected on the left side.

Previous studies suggest that gait is more asymmetric in patients with FOG when compared to patients without FOG. It has been hypothesized that a higher degree of asymmetry may lead to the development of FOG in PD [16]. It is well known that the basal ganglia are involved in automatic movement [17, 18] and that they provide phasic cues to the supplementary motor area, which regulates the control of gait [19, 20]. Impaired neuronal output from the basal ganglia to supplementary area can lead to an uncoordinated bilateral control of gait, which, at a certain level, may lead to FOG.

Fasano et al. [21] showed in PD with subthalamic deep-brain stimulation that the reduction of stimulation voltage in the side controlateral to the leg with longer step length improved frequency and duration of freezing of gait through a normalization of gait symmetry and coordination. The hypothesis of an influence of gait asymmetry on the pathogenesis of FOG might be linked to the “sequence effect” hypothesis, which suggests that episodes of FOG are determined by a progressive reduction in step length [22, 23]. In fact, gait asymmetry, associated with a progressive step length reduction, might lead to an increased likelihood to develop FOG through the “sequence effect” during overground walking [24]. Accordingly, one would expect higher levels of asymmetry in the FOG+ group of patients. We found that even though asymmetry tended to be higher in FOG+ patients, this trend was not statistically significant, and asymmetry of gait was observed also in patients without freezing. We argue that this lack of a clear difference between the two groups might be, at least in part, explained by the fact that the genesis of FOG is multifactorial: only when the global level of deterioration crosses a critical threshold, FOG manifests [24].

The hypothesis of a direct involvement of the asymmetry of gait in the development of FOG is also supported by our data on the efficacy of treadmill training on FOG. After the training, patients with FOG improved significantly the score at FOGQ and this improvement was significantly correlated to a reduction in the level of asymmetry.

Another novel interesting finding is the fact that asymmetry seems to have a dominant side, regardless of the side of disease. In fact, patients with prevalent right-side disease showed a marked asymmetry toward the left side, while the asymmetry toward the left side in patients mostly affected on the left side was confirmed as a trend but the difference was not statistically significant. These findings support the hypothesis of a prevalent involvement of the dominant hemisphere in PD [25, 26].

The mechanism by which treadmill training improves asymmetry of gait might be associated with the fact that treadmill with cues helps the patients by the feedback received from the treadmill, to correct the asymmetric step. This exercise allows the patient a progressive reduction of gait asymmetry.

Johnsen and colleague obtained similar results using the DBS of the subthalamic nucleus: when the DBS was ON, patients improved stride length, gait velocity, and reduced asymmetry between the right and left side. The authors concluded that it is possible to reduce asymmetry of gait and to improve balance using DBS [27].

Also in our study, an improvement of balance after the rehabilitation treatment was observed, and the improvement was better in FOG+ patients.

Indeed, at the end of treatment, both groups of patients showed an improvement in all the parameters used to evaluate the efficacy of training. Besides BBS, the FOG+ patients showed a better improvement also for UPDRS II. These data confirm the previous studies on the efficacy of a treadmill to improve autonomy in daily life [28, 29].

There are two different mechanisms likely to be involved in these results: a central and a peripheral role of treadmill on asymmetry of gait and freezing. The first mechanism is related to the effect that an intensive treadmill treatment might have on neuroplasticity. Both in unilateral and bilateral models of PD, intensive treadmill exercise produced improvement in motor symptoms, which was related to a reduction in the neurochemical deficit [30–33]. An increase in DA D2 receptors in the striatum was demonstrated by means of positron emission tomography imaging in MPTP treated mice after high-intensity treadmill exercises [34]. Overall, these findings show that intensive exercise exerts beneficial effects on DA transmission in parkinsonian mice models. These neuroplastic effects of intensive exercise are probably related to an increased expression of several neurotrophic factors, in particular brain-derived neurotrophic factor (BDNF) and glia-derived neurotrophic factor (GDNF) [35–38].

The second mechanism is related to a possible positive action on the spinal pattern generators (SPGs), which can produce automatic walking independent of higher central nervous system control. SPGs produces contraction/inhibition patterns within different muscle groups by alternating bursts to inhibit each other so that only one is active at a time [39]. Treadmill associated with cues might lead to an improvement of this mechanism in PD.

The FOG is one of the most important challenges in the treatment of PD. Our data indicate that treadmill training is effective in improving asymmetry of gait and balance in PD and in improving freezing in FOG+ patients. We speculate that this improvement might be related to a reduction in the level of asymmetric gait, thus providing new ideas for the development of therapeutic rehabilitative strategies to improve the quality of life in these patients.

Study limitations

Since gait speed, stride length, and time spent on each foot were computed using the motorized treadmill, the extrapolation of obtained results to overground walking is not straightforward.

For example, gait asymmetry as computed in this study, is an "average value" obtained during steady walking on the treadmill. This is quite different from asymmetry as observed during the sequence effect [22], where a time-varying phenomenon is considered and the progressive increase in asymmetry as stride length shortens till freezing takes place is studied. We argue that the degree of asymmetry could be higher in the steps immediately preceding the appearance of FOG. This could be another reason to explain why the differences we observed in gait asymmetry between the two groups did not reach statistical significance.

However, we also considered gait parameters such as CGS, FGS, and the 6MWT, which were carried out with the patients walking in a straight line in a gymnasium, without using cues. Our results indicate that these parameters also show an overall improvement. Moreover, several papers from us and different groups demonstrated that gait improvement achieved with treadmill translates to overground gait, and that beneficial effects persist over time.

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical standards All studies carried out in our Institution are in accordance with the ethical standards laid down in the Declaration of Helsinki and all participants give their informed consent prior to their inclusion in the study.

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