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# A 12-year population-based study of freezing of gait in Parkinson's disease

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ABSTRACT

*Introduction:* Freezing of gait (FOG) is a potentially disabling motor problem in Parkinson's disease (PD) with uncertain etiology. Longitudinal studies of FOG in PD are scarce. We determined the prevalence, incidence, and associated clinical risk factors and concomitants of FOG during prospective long-term follow-up of a population-based PD cohort.

*Methods:* A community-based prevalent cohort of 232 PD patients was followed prospectively over 12 years. Reassessments were conducted at 4 and 8 years, and then annually. FOG, as well as severity of parkinsonism, motor complications, and psychotic symptoms were assessed by the Unified PD Rating Scale, and cognitive impairment by the Mini-Mental State Examination. Generalized estimating equations were applied to investigate baseline risk factors and concomitants of FOG over time.

*Results:* The point prevalence of FOG at baseline was 27% (95% confidence interval (95%-CI) 22–33%). By study end, 63% (95%-CI 56–69%) of patients had developed FOG. The incidence rate of FOG was 124.2 (95%-CI 101.5–152.1) per 1000 person-years. Motor fluctuations (odds ratio (OR) 3.45; $p = 0.036$) and higher levodopa dose (OR 1.30/100 mg, $p = 0.009$) at baseline were independent risk factors of incident FOG. Prevalent FOG over time was additionally associated with features thought to reflect extrastrial, non-dopaminergic pathologies, including PIGD (postural instability/gait difficulty, OR 6.30/10 points, $p < 0.001$) and psychosis (OR 1.85; $p = 0.016$).

*Conclusion:* These findings demonstrate that FOG affects the majority of patients in the general PD population and provide support to the hypothesis that alterations in both basal ganglia and extrastriatal brain areas are involved in the pathogenesis of FOG in PD.

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## 1. Introduction

Freezing of gait (FOG) may become a challenging motor problem in patients with Parkinson's disease (PD). FOG describes a paroxysmal gait disturbance characterized by brief episodes of gait arrest resulting in inability to start or continue walking, particularly while turning [1]. The pathophysiology of FOG is complex, probably involving multiple brain and brainstem regions involved in locomotion, yet the exact neurobiological mechanisms are poorly understood [1].

FOG has been studied by a number of cross-sectional studies which find it to be a frequent complaint in PD. However, reported prevalence rates are derived from clinic-based samples, drug trials or patient surveys, and vary considerably from 31 to 87% [2–7]. Although some few longitudinal studies of FOG have been conducted in PD [3,5,8], none was population-based. In addition, incidence rates of FOG, which are considered a more accurate measure than prevalence rates, have to our knowledge not been reported in PD.

FOG in PD is associated with increased risk for falls [9], loss of independence [9], and impaired quality of life [7]. Hence, early identification of those who are at risk of developing FOG would be valuable for patients, caregivers, and health care planning. However, little is known about clinical risk factors for FOG, and results are conflicting: while increased motor severity, absence of tremor, and presence of gait disorder at disease onset predicted incident

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FOG during 18 months of follow-up in the seminal DATATOP study [3], a more recent 10-year clinic-based study failed to identify any predictors of FOG [5].

More detailed knowledge on the frequency, predictors and concomitants of FOG in PD would be important for patient management and may also provide new insights into underlying pathophysiological mechanisms. We here present the long-term course and associated risk factors and concomitants of FOG in a well-characterized, population-based PD cohort that was followed prospectively over a 12-year period.

## 2. Methods

### 2.1. Patients

All patients are participants in the Stavanger Parkinson project [10]. This project was initiated as a population-based cohort study in 1993 to estimate the prevalence of PD in Rogaland County, Western Norway, and was extended by prospective follow-up in subjects who consented in long-term participation. The study protocol was approved by the Regional Committee for Medical Research Ethics, Western Norway.

Details on case ascertainment and diagnostic procedures are previously published [10]. Briefly, of about 400 individuals who were identified through search of hospital files and multiple sources in the community (general practitioners, nursing homes, district nurses, patient organizations) and examined by movement disorder neurologists, 245 subjects were diagnosed with PD [11], and 239 of the 245 patients (98%), consented in study participation. During follow-up, seven patients were re-diagnosed as not having PD and excluded. Thus, 232 patients whose PD diagnosis remained unchanged were eligible for this long-term study of FOG in PD. A subgroup (n = 27) of the enrolled patients underwent autopsy. In all of these, the clinical diagnosis of PD was confirmed neuropathologically.

### 2.2. Examination program

The cohort was followed prospectively from 1993. Standardized re-assessments were conducted after four and eight years, and thereafter annually until 2005. At each study visit, a movement disorder neurologist from the study group conducted semi-structured interviews to assess demographic variables, medical history and medication use, and uniform clinical examinations to assess various motor and non-motor symptoms (see below). To minimize loss to follow-up of those with advanced disease, patients not able to visit the outpatient clinic were examined at their homes or nursing homes.

#### 2.2.1. Motor- and non-motor symptoms

Disease severity was measured by the Hoehn and Yahr staging (HY). The Unified Parkinson's Disease Rating Scale (UPDRS) [12] parts I to IV, which have been shown to strongly correlate with the corresponding parts in the more recently developed MDS-UPDRS [13], were performed to assess various motor and non-motor aspects related to PD.

UPDRS part III (motor section, items 18–31, potential score range 0–108, higher scores indicating more severe parkinsonism) was used for rating of overall parkinsonism severity and severity of tremor (items 20–21, score range 0–28), rigidity (item 22, score range 0–20), bradykinesia (items 23–26, 31, score range 0–36), and PIGD (postural instability/gait difficulty) (items 27–30, score range 0–16).

FOG was assessed using the UPDRS part II (ADL section), item 14 (score range 0–4), and was defined present if the score was ≥1, comprising rare, occasional, or frequent freezing episodes when walking, including start hesitation. Motor complications were assessed by the UPDRS part IV (complications of therapy). Dyskinesias were deemed present if items 32 (score range 0–4) or 33 (score range 0–4) were ≥1. Motor fluctuations were defined as presence of predictable wearing-off (item 36, score range 0–1) or unpredictable off periods (item 37, score range 0–1).

Psychosis was defined present if UPDRS part I, item 2 (score range 0–4) was ≥2, indicating hallucinations with or without insight retained, or delusions. Cognitive impairment was assessed by the Mini-Mental State Examination (MMSE, score range 0–30, lower scores indicating more severe cognitive impairment).

#### 2.2.2. Medication

Treatment of motor and non-motor symptoms followed best clinical judgment. Current medications were recorded at each study visit. Levodopa equivalent doses (LED) were calculated separately for the different levodopa formulations and dopamine agonists, according to published recommendations [14,15], using the following formula: LED = (regular levodopa dose × 1) + (levodopa controlled release dose × 0.75) + (pramipexole dose × 67) + (ropinirole dose × 16.67) + (pergolide dose and cabergoline dose × 67) + (bromocriptine dose × 10) + ((regular levodopa dose + levodopa controlled release dose × 0.75) × 0.25) if taking tolcapone or entacapone.

### 2.3. Statistical analysis

The incidence rate of FOG was calculated using standard methods by estimating the number of incident cases with FOG divided by the number of person-years at risk. Person-years at risk were estimated as the total follow-up time until incident FOG, dropout, death, or study end for those still free from FOG at end of follow-up. The date of onset of FOG, dropout or death was set to the midpoint between the study visits prior and after the event. 95% confidence intervals (CI) for incidence rate were calculated by the Poisson exact test, and for prevalence rates by the binominal exact test.

Population-averaged logistic regression models for correlated data, generalized estimating equations (GEE), were applied to identify independent risk factors for incident FOG (model 1) and concomitants of FOG during the study period (model 2). Odds ratios (OR), 95% CI, and Wald p-values based on robust estimation of the covariance matrix of the estimated coefficients are reported. In both models, FOG was included as dependent variable and the exchangeable correlation structure was run. Model 1 included patients without FOG at baseline who had at least one follow-up observation. Predictor variables in this model were age at motor onset, sex, and follow-up time, and baseline values for disease duration, UPDRS motor score, motor fluctuations (present or absent), dyskinesias (present or absent), psychosis (present or absent), MMSE, Levodopa LED, and dopamine agonist LED. Model 2 comprised all patients in the cohort and included the following independent variables at each visit during the study period: age at motor onset, sex, disease duration, UPDRS motor score, motor fluctuations (present or absent), dyskinesias (present or absent), psychosis (present or absent), MMSE, Levodopa LED, and dopamine agonist LED. Seven patients underwent subthalamic nucleus deep brain stimulation during follow-up due to intractable, disabling motor complications. As this intervention was considered as a potential confounder, post-surgery observations for these subjects were omitted from all analyses. Supplemental analyses were conducted as indicated below.

Two-tailed p-values <0.05 were considered statistically significant. Statistical analyses were performed using the statistical software program R 2.10.1 (The R Foundation for Statistical Computing, Vienna, Austria). The exact tests used the functions pois.exact and binom.exact in the package epitools. The regressions used the function gee in the package gee, with family 'binominal' for logistic regression with logit link and correlation structure 'exchangeable'.

## 3. Results

### 3.1. Baseline characteristics

The baseline characteristics of the 232 patients included in this study are given in Table 1. Mean (SD) age at motor onset was 64.9 (9.9) years and mean age at baseline was 73.5 (8.4) years. The majority of patients (75%) had mild to moderate disease (HY stage ≤3) at study entry.

**Table 1**
Demographic and clinical characteristics at baseline (n = 232).

| Characteristic | Value |
|---|---|
| Age at onset, years | 64.9 (9.9, 28.2–86.0) |
| Age, years | 73.5 (8.4, 35.4–93.4) |
| Disease duration, years | 8.6 (5.7, 0.5–33.4) |
| Male sex, n (%) | 113 (49) |
| UPDRS motor score | 28.7 (16.1) |
| Tremor score | 3.5 (3.4) |
| Rigidity score | 3.6 (3.2) |
| Bradykinesia score | 12.5 (7.2) |
| PIGD score | 5.9 (4.0) |
| Hoehn and Yahr stage | 2.8 (1.1) |
| Stage I–I.5, n (%) | 35 (15) |
| Stage II–II.5, n (%) | 79 (34) |
| Stage III, n (%) | 60 (26) |
| Stage IV, n (%) | 37 (16) |
| Stage V, n (%) | 21 (9) |
| Motor fluctuations, n (%) | 50 (22) |
| Dyskinesias, n (%) | 55 (24) |
| MMSE score | 24.3 (6.8) |
| Psychosis, n (%) | 39 (17) |
| Levodopa use, n (%) | 225 (97) |
| Dopamine agonist use, n (%) | 57 (25) |
| Levodopa LED, mg | 448 (227) |
| Dopamine agonist LED, mg[a] | 135 (74) |
| Total LED, mg | 479 (253) |

Values are mean (SD, range) or n (%).
[a] For patients on dopamine agonists.

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