



## Understanding falls in progressive supranuclear palsy



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### ABSTRACT

**Introduction:** Progressive supranuclear palsy (PSP) is characterized by frequent falls which worsen with disease progression, causing substantial morbidity and mortality. Few studies have investigated which factors contribute to falls in PSP, and all have involved few participants, thus lacking necessary statistical power. The aim of this study was to identify clinical parameters most significantly associated with increasing falls in PSP, using the largest sample of patients to date.

**Methods:** Comprehensive clinical data were collected from 339 not demented PSP patients meeting the NINDS-SPSP criteria, who were divided into two groups – Infrequent Fallers (IF; n = 118) with rare falls, and Frequent Fallers (FF; n = 221) who fell occasionally to multiple times a day. Of 198 clinical parameters, we hypothesized 38 to be correlated with an increasing risk of falls. These 38 parameters were analyzed via univariate regression analysis to determine the strength of their association with fall frequency. Unit odds ratios identified the magnitude with which each parameter resulted in an increasing risk of falls.

**Results:** Twenty-five of 38 parameters analyzed were significantly associated with fall frequency based on univariate analysis. Symptom duration, clinical measures of disease severity, and several motoric and oculomotor clinical parameters were associated with FF. Examined cognitive parameters and slowing of vertical saccades were not.

**Conclusions:** The clinical parameters identified as associated with increased frequency of falls improve our understanding of why they occur and may help identify not demented PSP patients at risk for increasing falls.

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## 1. Introduction

Progressive supranuclear palsy (PSP), an atypical parkinsonian syndrome, is characterized by falls early in the course of the disease. Patients typically present with progressive prominent postural instability with falls in the first year of onset and slowing of vertical saccades [1]. Other common clinical features of PSP

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include progressive akinetic-rigid axial parkinsonism with limited or no benefit from levodopa, early dysarthria and dysphagia, and frontal lobe disturbances. Although rare in the general population, it is the most common atypical Parkinsonian disorder; approximately 6% of all Parkinsonian patients evaluated at a specialty clinic are diagnosed with PSP [2].

The direct medical costs of falls among U.S. adults 65 years and older in 2000 amounted to 19.2 billion dollars [3]. It is therefore critical to identify factors that contribute to fall risks, especially in PSP where falls are an inherent part of the disease.

Few studies have investigated which factors contribute to falls in PSP [4–9]. This study evaluated which clinical parameters correlate with an increased risk of falls unrelated to freezing, using the largest sample of PSP patients to date.

## 2. Materials and methods

### 2.1. Subjects

Three hundred and fifty patients with a clinical diagnosis of PSP (289 probable, 39 possible and 22 eventually definite) according to the National Institute for Neurological Disorders and Society for PSP (NINDS-SPSP) criteria [1] were recruited for an epidemiological study investigating genetic and environmental risk factors for PSP (ENGINE-PSP) [10]. Data were prospectively and cross-sectionally collected by movement disorder specialists at 15 centers throughout North America following a standardized protocol. The ENGINE-PSP study excluded dementia or cognitive impairment that could have interfered with recall of life events. Therefore, participants in this study either scored  $\geq 24$  on the Mini-Mental Status Exam (MMSE), or between 21 and 24, but were deemed not demented by the site principal investigator (7%). Twenty-five patients underwent autopsy: 22 (88%) were pathologically confirmed to have PSP (definite); two had corticobasal degeneration presenting with a PSP phenotype, and one had undetermined pathology. These three patients were excluded from our analysis.

Patients were comprehensively evaluated with 196 clinical and historical parameters from the Unified Parkinson's Disease Rating Scale (UPDRS), PSP Rating Scale (PSPRS), Modified Hoehn & Yahr Staging Scale, Frontal Assessment Battery (FAB), Dementia Rating Scale (DRS), MMSE, California Verbal Learning Test (CVLT), and Neuropsychiatric Inventory (NPI). Two novel clinical parameters were also performed: "modified turning" and "posture – hyperextended". Modified turning evaluates a patient's propensity toward imbalance and subsequent falls upon turning (Table 1), while posture – hyperextended evaluates the axial extension and retrocollis commonly seen in PSP (Table 2).

Patients who scored a "4" on the UPDRS II question #15 'walking', indicating an inability to walk, even with assistance ( $n = 6$ ) or with missing data ( $n = 3$ ) were excluded, leaving a total of 339 patients for analysis.

Based on the UPDRS II question #13 'Falling unrelated to freezing', which evaluates how often patients have fallen within the last month, 339 patients were classified into two groups: Infrequent Fallers (IF) scored 0–1 ( $n = 118$ ), indicating no or rare falls; and Frequent Fallers (FF) scored 2–4, indicating occasional or daily

**Table 2**  
Posture – hyperextended question.

0	Not Hyperextended
1	Slightly hyperextended
2	Moderately hyperextended (few degrees), definitively abnormal
3	Severely hyperextended posture (several degrees)
4	Marked hyperextension with extreme abnormality of posture

falls ( $n = 221$ ). This item was chosen to quantify falls as FF and IF have been distinguished based on number of falls in the last month in similar studies, previously [7]. All procedures were approved by local institutional review boards at all ENGINE-PSP sites prior to commencing study procedures. All study participants provided written informed consent prior to data collection.

### 2.2. Statistical analysis

We performed univariate logistic regression analyses on 38 out of 198 parameters we hypothesized to be correlated with falls, to determine the strength of their association with the fall frequency expressed as a binary dependent variable. Correlations were considered significant at a  $p$ -value  $\leq 0.05$ .

Unit odds ratios measuring the strength of an association between a variable and its outcome were calculated with 95% confidence intervals, to compare the magnitude of various risk factors associated with falls.

Medications potentially contributing to falls that were taken by more than 5% of both FF and IF were also evaluated for their association with fall frequency using the Fisher exact probability test.

## 3. Results

Table 3 shows the demographics and clinical parameters of FF and IF. There were no significant between-group differences in age, sex, education, race, MMSE, and FAB total scores. However, symptom duration and indicators of non-cognitive disease burden (Total PSPRS, UPDRS Motor, and UPDRS Total) were significantly higher for FF.

Twenty-five of the 38 clinical parameters analyzed were significantly associated with fall frequency based on univariate analysis (Table 4). Symptom duration and clinical measures of disease severity (Modified Hoehn & Yahr Stage, Total and Motor UPDRS scores, PSPRS scores) were associated with FF; examined cognitive parameters (Total MMSE score, Total and subitem FAB scores, and Dementia Rating Scale subitem scores) were not. Motoric clinical parameters including postural stability, arising from a chair, and modified turning were associated with FF. Oculomotor parameters including horizontal saccades and eyelid apraxia/dystonia were associated with FF, while vertical saccades were not.

Unit odds ratios of the 25 parameters significantly associated with FF are shown in Table 5. As an example, for each one-unit worsening of the 'gait' score, the odds ratio of the patient becoming a FF increases by 1.7, and a 70% increase in the unit odds ratio is expected. Of note, parameters with a smaller range of possible scores have an inherently higher unit odds ratio. For

**Table 1**  
Modified Turning Question – Ability to turn 180° from a standing position.

0	Absent
1	Slow or Hesitant Turning
2	Turning "en-bloc", turning with motor blocks or pivoting (a tendency to drag the leg opposite the direction of turning) while turning, but without falling
3	'2' plus a tendency to fall while turning
4	Cannot turn without assistance

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