Original Article

Semantic Fluency Predicts Gait Velocity in PSP

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Abstract

Context: Progressive supranuclear palsy (PSP) is a large-scale network disease resulting in variable signs and symptoms including gait impairment and higher order cognitive dysfunction. Despite few studies showing the association of falls and cognitive dysfunction, the existing literature is yet to establish the exact relationship of discrete characteristics of gait with cognitive function in PSP. **Aims:** In this cross-sectional study, we aimed to characterize and explore the relationship of these two apparently distinct physiological phenomena in patients with PSP and across its different variants. **Methods and Material:** Quantitative assessment of two-dimensional gait parameters was measured using an electronic walkway (GAITRite®). Dementia Rating Scale-2 was used to assess global as well as higher order cognitive functions. **Statistical Analysis Used:** A regression model was used to interpret results. **Results:** We observed that the variability domain of gait was significantly impaired in PSP patients with severe cognitive impairment compared to that of intact cognition. Moreover, initiation/perseveration (I/P), a higher order cognitive process, and one of its specific components, i.e., complex verbal task ($\beta = 2.39$, $P < 0.001$), significantly predict gait velocity in PSP [F (1, 40) = 16.102, $P < 0.001$]. **Conclusions:** Our findings indicate that the severity of cognitive functions affects gait variability, which might lead to frequent falls as observed in PSP. Furthermore, semantic fluency task of I/P function may act as a predictor of gait velocity. We suspect that higher order cognitive dysfunction through the damage of frontal lobe structure including dorsolateral prefrontal cortex or related network may influence gait in PSP.

Keywords: Cognitive function, gait, initiation/perseveration, progressive supranuclear palsy

Introduction

Progressive supranuclear palsy (PSP) is an age-related neurodegenerative disease. Both aging and disease pathology may contribute to the changes in different brain areas and related circuits resulting in variable signs and symptoms including gait impairment over time across different phenotypes of PSP. Gait can be represented by multiple discrete characteristics, under the influence of different neural components. As a result, it is likely to respond in a selective manner to aging and pathological conditions.[1] In addition, gait can also be modulated through brain areas responsible for higher order cognitive process or executive functions (e.g., attention and memory).[1,2] Therefore, understanding the precise nature of neural control of PSP gait by exploring the link between gait and cognition might reveal new insights of the disease process. Despite few studies showing association of falls with cognitive dysfunction, the exact relationship of specific characteristics of gait with cognitive and executive function in PSP and across its different variants is still unknown.[3] We hypothesized that specific higher order cognitive functions influence discrete gait characteristics in PSP. In this cross-sectional study, we aim to characterize the nature of gait and higher order cognitive functions in PSP and its different variants. Additionally, we want to explore the relationship between different domains of gait and cognitive functions in patients with PSP.

Subjects and Methods

The study was approved by the institutional ethics committee and written informed consent was obtained from all the study participants. Fifty consecutive diagnosed cases of PSP patients classified into different PSP subtypes according to the Movement Disorder Society (MDS) criteria were recruited from the movement disorder outpatient department of a tertiary care neuroscience institute in India.[4] Gait analysis through GAITRite® and cognitive assessments through Mattis Dementia Rating Scale-2 (DRS-2) were done. Mattis-DRS-2 was used to examine global and different higher levels of cognitive function, i.e., attention (ATT), initiation/perseveration (I/P), construction (CONST), conceptualization (CONCEPT), and memory (MEM).[5] Motor severity was assessed using the MDS Unified Parkinson's Disease Rating Scale part III.[6]

For quantitative estimation of two-dimensional spatio-temporal gait parameters, subjects were instructed to walk four times

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successively at a self-selected normal pace on a 500-cm long electronic walkway (GAITRite®, CIR Systems, Inc., Franklin, NJ, USA), which had pressure sensors embedded in it. Gait outcomes were represented using the gait model developed by Lord *et al*., 2013.[7] Based on this model, different gait parameters were distributed amongst the five gait domains, i.e., pace, rhythm, variability, asymmetry, and postural control. From each domain, five representative gait parameters (velocity, swing time, step length variability, step time asymmetry, and step width) were selected for further investigation, as all the gait parameters from a given gait domain are comparable in our study [Supplementary Table S1].

Data were analyzed using SPSS Version 20 (IBM, Armonk, NY, USA). The normality of the data was examined using Shapiro–Wilk test. Velocity, step length, and step width showed normal distribution, whereas other gait parameters and cognitive measures (total DRS score, scores of ATT, I/P, CONST, CONCEPT, and MEM) were not normally distributed. One-way ANOVA was used to determine if significant differences in mean score of parametric gait variables exist across "intact," "mild," "moderate," and "severely" impaired group of PSP, whereas Kruskal–Wallis ANOVA was done to understand if significant differences in mean score on all the nonparametric gait variables exist across these cognitive categories. The number of patients in each of the subtypes other than PSP with Richardson's syndrome (PSP-RS) and PSP with Parkinsonism (PSP-P) was negligible in our sample. Moreover, PSP-RS are the most predominant phenotype followed by PSP-P, as expected. Therefore, we decided to restrict ourselves for further analysis with PSP-RS versus PSP-P and PSP-RS versus PSP-non-RS groups. Unpaired *t*-test was used to compare the means for all three normally distributed gait parameters in these subtypes and Mann–Whitney *U*-test was used to compare the difference between the same groups for all other gait parameters and cognitive measures. Associations between all cognitive and gait measures were first examined using Spearman's correlation followed by partial correlations, where age, disease duration, LEDD, and postural instability were used as covariates. No significant differences were noted on pairwise comparison between the left and right sides of the gait parameters. So, right-sided gait parameters were taken for further statistical comparison and data representation in tables and figure. Finally, multiple linear regression analysis was implemented to explore major determinants of gait parameters, based on the result of partial correlation. All data were reported as means and SD unless otherwise stated. *P* values of <0.05 were considered statistically significant for all the statistical tests.

Results

The mean age of all 50 patients was 64 ± 7 years with the disease duration of around 3 years. Seventy two percent of the patients was male. As expected, PSP-RS (60%) was the most predominant phenotype followed by PSP-P (22%). Among all of them, 42 patients were categorized into (1) intact, (2) mildly impaired, (3) moderately impaired, and (4) severely impaired cognitive groups based on Mattis-DRS-2 AMSS total scores. Variability gait domain was observed to be significantly impaired among PSP with four different cognitive categories mentioned above [Table 1 and Supplementary Table S1]. Kruskal–Wallis ANOVA revealed that more gait variability occurred in a severely impaired cognitive group as compared to the intact group (6.46 ± 4.73 versus 3.00 ± 1.04, $P < 0.01$). However, no significant differences were observed in any of the gait parameters between two principal PSP variants (PSP-RS versus PSP- *P* and PSP-RS versus PSP-non-RS).

Among all the five cognitive functions, only the impaired I/P group significantly differed from that of intact group. Unpaired *t*-test showed that impaired I/P had reduced velocity ($P = 0.001$, ES = −1.09), wider step width ($P = 0.007$, ES = 0.85), and more gait variability ($P = 0.007$, ES = 0.73) compared to having intact I/P [Figure 1]. Like gait parameters, we did not observe any significant differences in any of the cognitive functions between two principal PSP variants (PSP-RS versus PSP- *P* and PSP-RS versus PSP-non-RS).

Partial correlations showed significant association between different domains of gait and cognitive functions [Table 2]. Pace domain of gait was positively correlated with I/P ($r = 0.42$, $P = 0.014$). Gait variability was shown to be negatively correlated with global cognitive function ($r = −0.47$, $P = 0.006$), attention ($r = −0.44$, $P = 0.010$), initiation/perseveration ($r = −0.47$, $P = 0.006$), and conceptualization ($r = −0.50$, $P = 0.003$) as well. Postural control was also negatively correlated with I/P ($r = −0.42$, $P = 0.016$). Multivariate regression models suggested that I/P ($\beta = 1.29$, $P = 0.003$) was the predictor of gait velocity [R2 = 0.324, F (5, 31) = 2.97, $P = 0.026$] above and beyond age, disease duration, postural stability, and LEDD. Further analysis revealed that among six different components of I/P, complex verbal task ($\beta = 2.39$, $P < 0.001$) was the only one that can significantly predict gait velocity in PSP [F (1, 40) = 16.102, $P < 0.001$].

Discussion

The present study comprehensively explores the relationship of discrete gait characteristics with various higher order cognitive process or executive functions in a large cohort of well characterized PSP patients.

Gait variability of PSP is associated with higher order cognitive functions

In this study, we observed that the gait variability progressively deteriorated with the increasing severity of cognitive impairment in PSP patients. In congruence with our findings, Beauchet *et al*.[8] found that gait variability was higher even in mild stage of Alzheimer's disease in comparison with cognitively healthy individuals. Similarly, Hausdorff *et al*.[9] showed that gait variability was associated with disease severity, disease duration, and fall risk in PD. Lord *et al*.[7] reported a larger gait variability in older adults without apparent neurological disorders, although a similar correlation

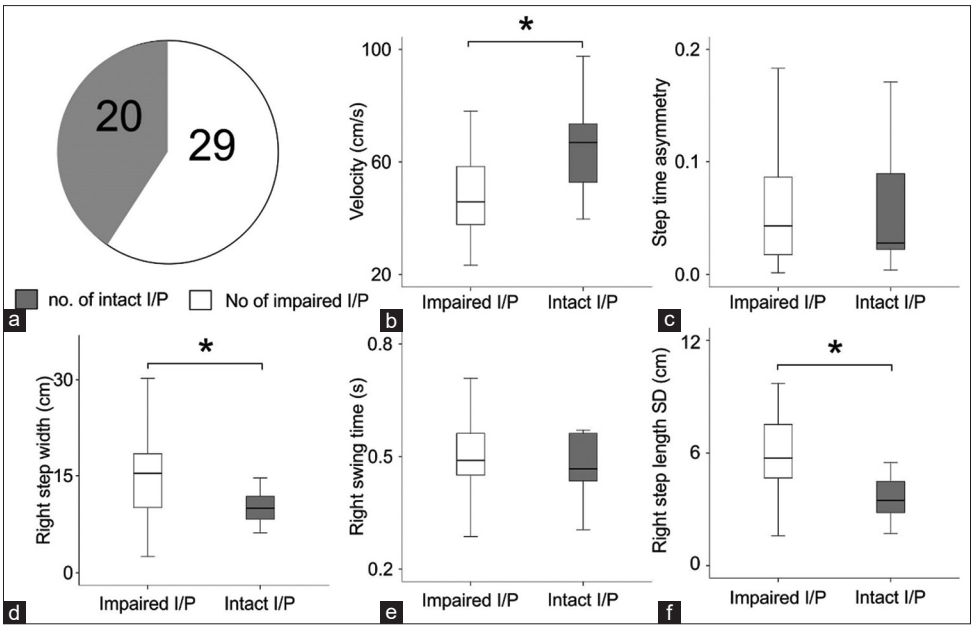

Figure 1: Comparison of gait parameters in impaired versus intact initiation/perseveration. (a) Pie chart distribution of total numbers of PSP patients with intact I/P and impaired I/P. Two-tailed independent *t*-tests were used for comparing (b) velocity, (c) step time asymmetry, (d) right step width, (e) right swing time, and (f) right step length SD between PSP patients with impaired and intact I/P. Data are presented as box plots. Error bar depicts standard error of mean. The *P* values were analyzed using two-tailed independent *t*-test. $P<0.05$ considered significant *. SD, standard deviation

Table 1: Gait characteristics of PSP with different cognitive categories. Of the 43 patients, we could not perform the cognitive assessment through DRS-2 on one patient. Thus, when categorizing patients into different cognitive groups the total *n* became 42

Gait Domains	Selective Gait Parameters	Patients (*n*=43)	Clinical Interpretation as per DRS 2 AMSS Total Scores				*P*
			Intact (*n*=5)	Mildly Impaired (*n*=3)	Moderately Impaired (*n*=9)	Severely Impaired (*n*=25)	
Pace	Velocity (cm/s)	54.74±17.43	63.32±14.73	57.47±13.42	60.53±21.28	51.08±16.75	0.35
Rhythm	Right swing time (s)	0.39±0.11	0.40±0.10	0.39±0.04	0.35±0.08	0.41±0.12	0.37
Variability	Right step length SD (cm)	5.28±3.96	3.00±1.04	3.15±1.01	4.03±1.82	6.46±4.73	**<0.01**
Asymmetry	Step time asymmetry	0.07±0.07	0.02±0.03	0.08±0.07	0.09±0.09	0.08±0.06	0.18
Postural control	Right step width (cm)	13.38±5.74	11.55±4.32	11.02±2.90	11.85±8.16	14.3±5.16	0.53

n, sample size. Data are presented as mean±standard deviation. The *P* values were analyzed using one-way ANOVA test. SD, standard deviation; $P<0.01$ considered significant (indicated in bold)

Table 2: Partial correlation for cognitive and gait domains

Gait Domains	Gait Parameters	PSP (*n*=42)
Pace	Velocity (cm/s)	0.42 (*P*=0.014) I/P
Variability	Right step length SD (cm)	−0.47 (*P*=0.006) DRS −0.44 (*P*=0.010) ATT −0.47 (P=0.006) I/P −0.50 (P=0.003) CONCEPT
Postural control	Right step width (cm)	−0.42 (*P*=0.016) I/P

Age, disease duration, LEDD, postural instability included as covariates. DRS, DRS-2. AMSS total score; ATT, attention AMSS score; I/P, initiation/perseveration AMSS score; CONCEPT, conceptualization AMSS score

was not evident in healthy young individuals.[10] Hence, it is obvious that an intact cognitive function is essential for healthy walking and gait variability is altered in the early stage of cognitive impairment. We further showed that reduced function of specific cognitive domains like attention, initiation/perseveration, and conceptualization in PSP were correlated with the increasing step-to-step variability.

Dual task while walking is one of the established methods to perturb the attention domain of cognition. Due to reduced attention, PD patients displayed a greater gait variability while performing an additional task during walking.[11] In another study, stride time variability increased from 0.04 s to 0.2 s when they were instructed to walk with a cognitive load ($P<.002$).[9] Sheridan *et al*.[12] also observed that gait variability is larger while performing more than one task simultaneously in patients with Alzheimer's disease. All these studies reinforce our finding that attention carries a remarkable effect on gait variability. Determining a cause-effect relationship between higher order cognitive functions and gait variability is beyond the scope of this cross-sectional study.

The clinical significance of gait variability is quite profound. The increase in gait variability might originate from the lack of postural control. As a consequence, fall was found to be associated with a higher gait variability in various neurodegenerative conditions including PD.[13,14] Perhaps, patients of PSP with high gait variability have more risk of falls, although we have not specifically investigated this question in our current study.

Impaired initiation/perseveration (I/P) may result in poor gait pattern

I/P is one of the higher cognitive process which is defined as a measure of executive functional capability to initiate a task through actively translating sensory information into verbal or motor action. Walking requires mental imagination and planning to initiate and execute the motor action using multimodal activity of brain–body interaction including coordination of different components of executive function. Hence, this study result indicates that increased step width might be a compensatory phenomenon for unstable postural control in PSP patients with impaired I/P as compared to those with intact I/P.

We further propose that significant slowness of PSP gait in patients with impaired I/P could be due to following reasons.

(i) A possible defense mechanism to prevent falls.
(ii) Networks of motor control (like gait) and higher order cognitive functions (mainly executive functions like I/P) are believed to be interlinked. Derangement of the common anatomical substrate including dorsolateral prefrontal cortex (DLPFC)[15] may result in impairment, as observed in our study.
(iii) Frontal lobe dysfunction can exhibit freezing of gait and subclinical delay in gait initiation process as observed in PD and PSP.[16]

Semantic fluency task and gait velocity in PSP

Our study findings reveal that complex verbal task (a semantic fluency test) of I/P predicts gait velocity in PSP. In semantic fluency test as seen in Mattis-DRS-2, participants are asked to utter as many items as possible within a stipulated period (e.g., to name grocery items within a minute). This task requires "visuo-spatial mental imagery strategy" formation through involvement of right dorsolateral prefrontal cortex (DLPFC).[17,18] DLPFC also encodes the goal or plan for movement while walking,[19] as some studies have explained that application of noninvasive brain stimulus to DLPFC significantly increases gait speed in PD.[20] Hence, we speculate that "visuospatial mental imagery strategy" might be involved in "locomotor imagery tasks," which activates frontal regions of the brain.[21]

Comparing gait among different psp variants

It is well-known that PSP variants are clinically classified based on their ocular motor dysfunction, postural instability, and akinesia. Contrary to our expectation, GAITRite® failed to capture the difference in gait parameters in PSP-RS and PSP-P. Perhaps, it indicates that gait in PSP may not solely depend on the above-mentioned clinical problems, rather other factors including higher order cognitive functions may also contribute to their gait. In further support to our hypothesis, we did not observe any significant differences in any of the cognitive process among PSP variants, which was contrary to the previous finding.[22] It may reconfirm that the null result of gait differences among PSP variants was not obtained by chance. Nevertheless, the actual reasons are yet to be deciphered.

Few limitations of the present study include cross-sectional study design, which does not allow us to predict causality and a time-dependent relationship between cognitive dysfunctions and gait impairment in PSP.

Our findings emphasize the level of involvement of cognitive function particularly executive function in goal-directed motor control during walking of PSP. It shows that variability and pace are two specific gait domains, which are primarily influenced by higher order cognitive process. This may help in the decoding neuronal process of PSP patients presenting with walking difficulty, balance problems, and executive dysfunction. We suspect that DLPFC may be the area to be targeted for gait improvement in PSP patients. We showed verbal semantic fluency to be a useful predictor of walking speed in our patients. There could be some overlapping neuronal process that control both word and gait processing through mental imagery strategy formation. Through this study, we gain the experience of using DRS-2 for cognitive assessments in PSP patients and we found it useful in predicting gait abnormality in PSP patients. Assessment through I/P section of DRS-2 takes not more than 5 minutes and this method for assessing cognition is widely used in research practice. We encourage the use of this tool by clinicians as we believe that the I/P section can be associated with gait impairment in PSP patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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