DOI: *http://dx.doi.org/10.18502/cjn.v23i1.???*

Current Journal of Neurology

Original Paper

Curr J Neurol 2024; 23(1): 66-73

Podcast

A study on possible risk factors for progressive supranuclear palsy in southern part of India

Received: 09 Sep. 2023
Accepted: 05 Nov. 2023

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Keywords
Case-Control Studies; Surveys and Questionnaires; Multivariate Analysis; Smoking; Progressive Supranuclear Palsy; Risk Factors

Abstract

Background: The etiological factors leading to progressive supranuclear palsy (PSP) are poorly understood. This study aims to evaluate the role of various risk factors in patients with PSP.

Methods: A case-control study was conducted over a period of two years from March 2016 to March 2018. The cases were recruited independently by two senior neurologists and a consensus was then reached after discussion for their inclusion. The controls were free of parkinsonian features or dementia and matched by age (± 3 years), sex, and race with the cases. The study population was then interviewed using a standard questionnaire for various possible risk factors. Variables with a significance (P ≤ 0.05) in univariate analysis were considered for bivariate analysis, multivariate analysis, and logistic-regression analysis.

Results: A total of 51 cases with an equal number of controls were included in this study. Ten separate variables that included poor educational status, well water, smoking, tapioca, bakery/fast food, tea ≥ 5 cups/day, personality, exposure to pets, exposure to cattle, and family history of stroke were found to show statistical significance after univariate analysis. Among these, tapioca consumption, fast food and bakery items consumption, type A personality, and family history of stroke were found significant after adjusting for the confounding factors.

Conclusion: The possible etiological factors that have a relevance in the causation of PSP as borne out in our study include dietary habits such as tapioca, fast food, and bakery items consumption, family history of stroke, and type A personality trait.

Introduction

Progressive supranuclear palsy (PSP) is an atypical parkinsonian syndrome characterised by supranuclear ophthalmoplegia, early gait instability, axial rigidity, dysarthria, dysphagia, and progressive dementia.

How to cite this article: Thomas AG, Mohan M, Thomas R. A study on possible risk factors for progressive supranuclear palsy in southern part of India. Curr J Neurol 2024; 23(1): 66-73.

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PSP is a four-repeat (4R) tauopathy and is characterised by globose neurofibrillary tangles (NFTs), tufted astrocytes (TA), neuronal loss, and gliosis. Tau-immuno-reactive lesions are observed in basal ganglia, brainstem, cerebellum, and diencephalon with restricted involvement of the neocortex primarily the precentral gyrus.[1]

PSP is relatively rare compared to Parkinson's disease (PD) and the age-adjusted prevalence noted in a population-based study was 6.4 per 100000.[2] We have observed that PSP is more frequent among the population in southern India, although there are no epidemiological studies to support this claim. Since its original description in 1964 by Steele et al.,[3] much work has been conducted on the clinical and pathological aspects of the disease. However, the etiological factors leading to this neurodegenerative disease remain poorly understood. The aim of the present study was to evaluate the role of various risk factors in patients with PSP.

Materials and Methods

This was a case-control study done at Pushpagiri Institute of Medical Sciences and Research Centre, a teaching institute located in southern part of India. It was conducted during a study period of two years extending from March 2016 to March 2018.

The diagnosis of PSP was made using the National Institute of Neurological Disorders and Stroke-Society for PSP (NINDS-SPSP) criteria for probable PSP.[4] It was defined as a progressive disorder with onset at the age of 40 or later with either vertical (upward or downward gaze) supranuclear palsy or both slowing of vertical saccades and prominent postural instability with falls in the first year of disease onset. All cases where neuroradiologic evaluation suggested alternative causes and those with a mini-mental state examination (MMSE) score less than 24/30 were excluded from the study.

Patients who visited the institute and who were diagnosed as PSP cases were recruited independently by two senior neurologists and the consensus was then reached. The controls were the bystanders of other patients, free of Parkinsonian features or dementia. They were matched by age (± 3 years), sex, and race with the cases. The controls were not related to any of the cases studied.

A structured questionnaire was administered to the PSP cases or their next of kin accompanying them and the controls by the first author. Questionnaires administered to five sets of cases and controls were randomly cross checked initially by the second and the third authors for the reliability of information collected. The questionnaire contained demographic details, past history, family history, dietary details, and exposure to other risk factors. The putative risk factors that were studied were chosen based on the current literature for risk factors for idiopathic PD (IPD), PSP, and other atypical parkinsonian syndromes. Smoking habit was classified into three categories on the basis of pack-years: never-smokers (0 pack-years), moderate smokers (< 30 pack-years), and heavy smokers (> 30 pack-years). The frequency of consumption of various dietary factors was used to quantify the risk involved.[5,6] We assumed the consumption of tapioca, fast food/bakery items, and carbonated drinks to be frequent if they were taken at least fortnightly. Fast food/bakery items were defined as foods prepared outside of home.[7] Fresh fruits and vegetables, dairy products, and tea or coffee (≥ 5 cups) consumption were considered frequent if they were taken on a daily basis. Personality type was assessed with a battery of questions.[8] The measure had 14 rating scales. Higher ratings indicated a higher degree of the presumed pattern A characteristics. The ratings were summed over the 14 items to obtain the rating score. In our study, if more than half were answered positively in a particular group, the subject was classified into that personality group. The authors together interpreted the questionnaire and entered the data into Microsoft Excel.

A written informed consent was taken from each subject enrolled in this study. The study protocol was approved by the institutional ethics committee.

Baseline characteristics were represented as frequency with percentage for categorical variables. Normality of the data was assessed using skewness, kurtosis, and by constructing histogram. Proportions were analysed using chi-square test and Fisher's exact test if any of cell frequency was < 5. The predictors of outcome were determined by univariate analysis. Variables with a significant P-value (≤ 0.05) in univariate analysis were considered for bivariate analysis, multivariate analysis, and logistic-regression analysis. Statistical analyses were performed using STATA software (version 15.0, Stata Corporation, College Station, TX, USA).

Results

Baseline characteristics: Fifty-one PSP cases and

an equal number of controls were recruited during the study period. The baseline characteristics such as age, sex, and occupation were similar in both case and control groups (P > 0.05). The age and sex were equally matched. The mean age at onset of symptoms was 62.2 ± 5.9 years and the mean age at presentation to our centre was 65.8 ± 6.2 years. Patients presented nearly 3.52 ± 1.60 years after the symptom onset. The classic PSP type comprised the majority (66.7%) of cases while the PSP type with the lowest frequency was PSP-corticobasal syndrome (3.9%). The other three types of PSP including PSP-parkinsonism, pure akinesia with gait freezing, and PSP-behavioural variant of frontotemporal dementia were all of similar frequency (9.8%). Poor educational status (middle school certificate and below) was significantly associated with risk of PSP (Table 1).

Relation between PSP and environmental exposures to toxins and occupation: The well water usage was found to be significantly higher in cases than in controls. The other variables were the same among cases and controls. Other variables did not show any significant association to the chance of acquiring the disease (Table 2).

Relation between PSP and dietary factors, personal habits, and other comorbidities: Consuming fresh fruits and vegetables, tapioca, fast food/bakery items, and taking 5 or more cups of tea per day were associated with 6.732, 8.382, 6.732, and 3.147 times risk of developing the disease, respectively. Other food consumption factors did not show any statistically significant association among the cases and controls (Table 3).

The patterns of addiction among the cases and controls were studied. Heavy smokers were high in the case group. Non-smokers were almost the same in both groups. Smoking was significantly associated with the cases, with 2.3 times the odds for having disease if the subject was a smoker. However, alcoholism was seen only in a small group with 10% in cases and 6% in controls (Table 3).

Type A personality was significantly associated with cases as compared to control. There was no significant association noted with other comorbidities (Table 3).

Relation between PSP and past and family history: Exposure to pets and cattle showed higher predisposition in cases (Table 4).

The family history of dementia, parkinsonism, and stroke showed a significant association between them and the chance of being the case.

Table 1. Demographic characteristics of progressive supranuclear palsy (PSP) cases and controls

Demographic characteristics	Total (n = 102) [n (%)]	Control (n = 51) [n (%)]	Case (n = 51) [n (%)]	P
Gender (n = 102)				> 0.999
Women	42 (41.2)	21 (41.2)	21 (41.2)	
Men	60 (58.8)	30 (58.8)	30 (58.8)	
Age at study (year) (n = 102)				0.623
51 to 60	19 (18.6)	11 (21.6)	8 (15.7)	
61 to 70	64 (62.8)	32 (62.7)	32 (62.7)	
71 to 80	19 (18.6)	8 (15.7)	11 (21.6)	
Occupation (n = 102)				0.379
Profession	6 (5.9)	3 (5.9)	3 (5.9)	
Semi-profession	12 (11.8)	5 (9.8)	7 (13.7)	
Clerical, shop-owner	27 (26.5)	13 (2.5)	14 (27.5)	
Skilled worker	18 (17.6)	10 (19.6)	8 (15.7)	
Semi-skilled worker	12 (11.8)	6 (5.9)	6 (5.9)	
Unskilled worker	8 (7.8)	7 (13.7)	1 (2.0)	
Unemployed	19 (18.6)	7 (13.7)	12 (23.5)	
Education (n = 102)				0.001
Profession or honours	2 (2.0)	1 (2.0)	1 (2.0)	
Graduate or postgraduate	12 (11.8)	6 (11.8)	6 (11.8)	
Post high school diploma	18 (17.6)	13 (25.5)	5 (9.8)	
High school certificate	25 (24.5)	14 (27.5)	11 (21.6)	
Middle school certificate	19 (18.6)	14 (27.5)	5 (9.8)	
Primary school certificate	26 (25.5)	3 (5.9)	23 (45.1)	
Educational status (n = 102)				0.020
Poor educational status	45 (44.2)	17 (33.3)	28 (54.9)	
High educational status	57 (55.8)	34 (66.7)	23 (45.1)	

Table 2. Relation between progressive supranuclear palsy (PSP) and environmental exposures to toxins and occupation

Environmental factors	Control (n = 51) [n (%)]	Cases (n = 51) [n (%)]	P
Using well water	20 (39.2)	35 (68.6)	0.003
Radiation exposure	0 (0)	1 (1.9)	0.315
Pesticide exposure	1 (1.9)	4 (7.8)	0.169
Insecticide exposure	1 (1.9)	6 (11.8)	0.510
Fertilizer exposure	11 (21.6)	11 (21.6)	> 0.999
Solvent/cleaning liquid exposure	0 (0)	3 (5.9)	0.079
Auto exhaust exposure	7 (13.7)	20 (39.2)	0.079
Contact sports	1 (1.9)	1 (1.9)	> 0.999
Head injury	1 (1.9)	5 (9.8)	0.092

The other family histories did not show any statistically significant association with the cases and controls (Table 4).

Binary logistic regression: In our study, the univariate analysis showed statistical significance to ten separate variables which included poor educational status, well water, smoking, tapioca, bakery/fast food, tea ≥ 5 cups/day, personality, exposure to pets, exposure to cattle, and family history of stroke. Binary logistic regression was done to create a model with the above exposure factors to the likelihood of the outcome of PSP (Table 5). The Cox and Snell R square value of 0.406 signified that the model predicted all the exposure variables had an 40.6% variance on the chance of being the case. The exposure variables of tapioca consumption, fast food/bakery items consumption, type A personality, and family history of stroke were found significant after adjusting for the exposure variables.

After adjusting for every confounding factor, we found out that for consumption of tapioca there was 7.694 [adjusted odds ratio (AOR)] times risk of patient to become the case. With fast food and bakery items consumption, there was a 10.395 times the risk involved. Type A personality and family history of stroke had 4.382 and 6.349 times the risk, respectively.

Odds ratio (OR) comparison between bivariate and multivariate analysis: The bivariate comparison showed all the variables to be significant and having generally higher OR for being the case. In multivariate analysis, there was only 4 variables with significantly high OR (Table 6).

Discussion

A case-control design was used to examine the role of a wide range of possible risk factors leading to PSP. We used a very detailed questionnaire exploring the various possible etiological factors to which the local population might have been exposed to.

Table 3. Relation between progressive supranuclear palsy (PSP) and dietary factors, personal habits, and other comorbidities

Dietary factors, personal habits, and other comorbidities	Control (n = 51) [n (%)]	Cases (n = 51) [n (%)]	P
Fresh fruits and vegetables	2 (3.9)	11 (21.6)	0.090
Tapioca	2 (3.9)	13 (25.5)	0.002
Fast food/bakery items	2 (3.9)	11 (21.6)	0.008
Dairy products	5 (9.8)	11 (21.6)	0.102
Carbonated drinks	2 (3.9)	4 (7.8)	0.400
Coffee ≥ 5 cups per day	2 (3.9)	4 (7.8)	0.400
Tea ≥ 5 cups per day	5 (9.8)	13 (25.5)	0.038
Non-vegetarian diet	47 (92.2)	44 (86.3)	0.338
Alcoholism	6 (11.8)	10 (19.6)	0.276
Smoking	6 (11.8)	24 (47.1)	< 0.001
Personality type A	7 (13.7)	20 (39.2)	0.004
Hypertension	19 (37.3)	26 (51.0)	0.400
Diabetes	31 (60.8)	31 (60.8)	> 0.999
Dyslipidemia	23 (45.1)	27 (52.9)	0.428
Coronary artery disease	11 (21.6)	17 (33.3)	0.183
Thyroid disease	5 (9.8)	10 (19.6)	0.162

Table 4. Relation between progressive supranuclear palsy (PSP) and past and family history

Past and family history	Control (n = 51) [n (%)]	Cases (n = 51) [n (%)]	P
Surgeries	5 (9.8)	5 (9.8)	> 0.999
More than 2 general anesthesia	2 (3.9)	1 (2.0)	0.558
Blood transfusion	2 (3.9)	4 (7.8)	0.400
Dentures	3 (5.9)	4 (7.8)	0.695
Dental procedures	4 (7.8)	9 (17.6)	0.138
Exposure to pets	7 (13.7)	17 (33.3)	0.020
Exposure to cattle	4 (7.8)	16 (31.4)	0.003
Family history of dementia	0 (0)	12 (23.5)	< 0.001
Family history of parkinsonism	0 (0)	9 (17.6)	0.002
Family history of epilepsy	4 (7.8)	8 (15.7)	0.219
Family history of stroke	3 (5.9)	15 (29.4)	0.002

In our study, poor educational status (middle school certificate and below) was significantly associated with risk of PSP. In an early study by Davis et al., it was reported that PSP cases had a higher education level than controls.[9] However, similar to what we have observed, Golbe et al.[10] and Vidal et al.[11] found an increased risk of PSP in subjects with a lower education level. Poor education, in turn, leads to lower socioeconomic status. Hence, we hypothesize that a possible toxico-nutritional etiology is responsible for the increased risk of PSP in such a situation. Dietary habits and probable higher chance of exposure to toxic elements in their environment poses a greater threat of disease in this population.

Well water consumption was significantly higher in PSP cases than the controls in our study. Rajput et al. found no differences in concentrations of either water metal concentration or any of the herbicides and pesticides used related to the cause.[12] Gatto et al. found evidence for consumption of well water potentially contaminated with pesticides to be a risk factor for PD.[13] James and Hall concluded that for every 1.0 µg/l of pesticide in groundwater, the risk of PD increased by 3%.[14] Although in our study, neither pesticides nor other chemicals were identified as occupational exposures, we believe that they may be a causal factor with the well water being the vehicle. Further studies to determine the composition of well water need to be undertaken in order to identify possible causal elements.

Our study also showed that PSP cases smoked more frequently than the matched controls. Prior case-control studies did not reveal differences in smoking habits between patients with PSP and control subjects.[11,15] However, in our study, smoking was not found to be significant after adjusting for the confounding factors.

Dietary habits in PSP were analysed in detail in our study unlike many of the prior studies. After adjusting for every confounding factor, we found out that for consumption of tapioca, there was 7.694 (AOR) times risk of patient to become the case. Tropical ataxic neuropathy (TAN) is a neurological syndrome attributed to toxiconutritional causes. Although initially it was proposed to be due to nutritional deficiency, the later reports suggested cassava (tapioca) neurotoxicity as the probable cause.[16,17]

Table 5. Binary logistic regression

Exposure variables	AOR	95% CI		P
		Upper limit	Lower limit	
Poor educational status	1.202	0.986	1.565	0.223
Well water	2.066	6.215	0.687	0.197
Smoking	4.069	23.993	0.690	0.121
Tapioca consumption	7.694	55.169	1.073	0.042
Fast food/bakery items	10.395	61.816	1.748	0.010
Tea ≥ 5 cups/day	2.525	12.124	0.526	0.247
Type A personality	4.382	15.556	1.235	0.022
Exposure to pets	3.019	11.140	0.818	0.097
Exposure to cattle	3.632	17.317	0.762	0.106
Family history of stroke	6.349	34.113	1.182	0.031

Cox & Snell R square: 0.406

AOR: Adjusted odds ratio; CI: Confidence interval

Table 6. Odds ratio (OR) comparison between bivariate and multivariate analysis

Exposure variables	Bivariate analysis		Multivariate analysis	
	OR	P	AOR	P
Poor educational status	1.542	0.020	1.202	0.223
Well water	3.390	0.003	2.066	0.197
Smoking	2.133	0.001	4.069	0.121
Tapioca	8.382	0.002	7.694	0.042
Fast food/bakery items	6.732	0.008	10.395	0.010
Tea ≥ 5 cups/day	3.147	0.038	2.525	0.247
Type A personality	4.055	0.004	4.382	0.022
Exposure to pets	3.142	0.020	3.019	0.097
Exposure to cattle	5.371	0.003	3.632	0.106
Family history of stroke	6.666	0.002	6.349	0.031

OR: Odds ratio; AOR: Adjusted odds ratio

Tapioca is consumed in large quantities in the area where we undertook our study. Madhusudanan et al. have described the occurrence of TAN in Kerala, India, and the possible etiological role of tapioca intake.[18] The age-specific prevalence of TAN was noted to be the highest in the elderly (60-69 years) age group which is similar to the PSP cases.[19] Hence, we propose that PSP may be due to localised neuronal damage that does not produce symptoms until after several decades of age-related neurodegeneration. A dose-response relation can be expected for neuronal damage of toxic origin in this case. However, we are unable to offer any satisfactory explanation to account for the different clinical presentations in these two diseases. Further large-scale studies are needed to confirm the etiological role of tapioca in PSP.

Other food items which showed significance after adjusting for confounding factors were the fast food and bakery items. In the area of our study, the items consisted mainly of either deeply fried meat products or foods high in added sugar. A case-control study on PD reported significantly increased OR for higher consumption of sweets, chocolate, and desserts.[20] Another study on PD found a non-significant decreased OR for higher junk food intake.[21] In PSP, a study by Vidal et al. reported that patients with PSP ate meat and poultry more often.[11] In our study, we found that with fast food and bakery item consumption, there was a 10.395 times the risk involved.

Coffee and caffeine intake has been associated with lower risk of PD in meta-analyses and large cohort studies.[22-24] However, in our study, no significant association was found with coffee consumption. Although univariate analysis showed statistical significance with consumption of tea ≥ 5 cups/day, it did not show significance after adjustment for confounding factors.

These results regarding dietary habits must be interpreted with caution. This is because retrospective assessment of dietary habits can be affected by recall bias and measurement errors.

The univariate analysis showed statistical significance with the exposure to pets and cattle. However, after adjusting for every confounding factor, it did not show any significance. None of the previous epidemiological studies have found this association, to the best of our knowledge.

Dubinsky and Jankovic had proposed a vascular etiology for some patients with PSP.[25] They reported that patients with PSP were more likely to have occurrence of one or more strokes than patients with PD. In our study, none of the cases or controls had a prior history of stroke. For questions concerning family history, prior stroke was more frequently reported in the families of cases, and it was statistically significant. However, as the majority of these relatives were all deceased, it was difficult to confirm the accuracy of the diagnosis. Larger studies will be needed to determine whether the same is true in PSP.

After adjusting for confounding factors, we found that type A personality was associated with 4.382 times risk of developing PSP. People with type A personality have increased anxiety and difficulty in handling stress. Stressors are well-known to activate the hypothalamic-pituitary-adrenal (HPA) axis. When body undergoes stress, cytokines are released which activate the HPA axis.[26] In patients with PD, it has been reported that there is increased concentrations of interleukins (ILs), tumour necrosis factor (TNF), interferon γ (IFN-γ), and β-2-microglobulin (β2m) mediating neuroinflammatory processes in their substantia nigra and striatum.[27] Risk of PD is reported to be increased in men with high plasma concentration

of IL-6 and decreased in people who take non-steroidal anti-inflammatory drugs (NSAIDs).[28,29] Hence, we believe that in people with type A personality trait, similar mechanisms likely contribute to neuronal damage in patients with PSP.

We acknowledge that the methodology which we have employed has certain limitations. As in every case-control study, there may be a recall bias involved in this study as well. The patients and the relatives while in hospital may have more chance to recall the risk factors. We tried to eliminate this bias by recruiting both cases and controls from our hospital population. The spouse or a close relative to the patient was also motivated to help the patient in answering the questionnaire. The study subjects were allowed to take ample amount of time before returning the questionnaire. Only those with MMSE scores > 24 were enrolled in our study to further eliminate this bias. This study could not detect associations with rare exposures due to the small sample size. There was no validated questionnaire available during the time of study and the risk factors were chosen based on previous similar studies done for various parkinsonian syndromes. Although the recruitment of cases and controls was done by senior neurologists, the questionnaire was administered by the first author who was at that time undergoing training in neurology.

Conclusion

Dietary habits such as tapioca and bakery and fast food consumption, family history of stroke, and type A personality trait, all were significantly associated with the causation of PSP. Evaluation of the composition of well water and the dietary items may better delineate their association with PSP. Future studies with larger number of patients need to be undertaken to further investigate the etiological factors in PSP. These findings may help develop future prevention and treatment strategies for patients with PSP and other parkinsonian disorders.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

None.

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