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Hypertension and progressive supranuclear palsy

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ABSTRACT

Background: The epidemiologic evidence of whether hypertension is associated with Progressive Supranuclear Palsy (PSP) is inconsistent. The ENGENE-PSP case-control study determined various PSP risk factors including whether hypertension preceded PSP onset.

Methods: Incident PSP cases per NINDS-PSP criteria and age-, sex-, race- matched controls were recruited from similar North American geographic areas. All study participants were administered standardized interviews to obtain data on demographics, medical history and medications.

Statistics: We used univariate and multivariate conditional logistic regression models to measure the associations between PSP and the following predictor variables: education level, hypertension, comorbid vascular conditions (diabetes mellitus and hyperlipidemia), and classes of anti-hypertensive medications using odds ratios and 95% confidence intervals.

Results: There were significant associations seen between PSP and hypertension (OR: 1.569; 95% CI 1.129–2.181; p-value = 0.007), education level (OR: 0.733; 95% CI 0.637–0.843; p-value < 0.001) and beta-blocker use (OR: 2.000; 95% CI 1.053–3.799; p-value = 0.034). However, in the multi-variate analysis hypertension (OR: 1.492; 95% CI 1.045–2.129; p-value = 0.027) and education level (OR: 0.730; 95% CI 0.633–0.841; p-value < 0.001) were the only significant associations.

Conclusion: These results suggest that there is a modest, yet significant association between hypertension and PSP. Further studies will be needed to better understand the pathophysiological basis for this finding.

1. Introduction

Progressive supranuclear palsy (PSP) is the most prevalent atypical neurodegenerative Parkinsonian disorder [1]. PSP is clinically characterized by postural instability, axial parkinsonism, vertical supranuclear gaze palsy and frontal dementia [2]. Neuropathologically, PSP is classified as a tauopathy in which abnormally phosphorylated tau-protein accumulates in neurons and glia in specific basal ganglia and brainstem areas. Currently, there are no treatments to slow disease progression and prognosis is poor with a median survival of approximately 6 years after symptom onset [1]. Several risk factors for developing PSP have been identified including genes such as MAPT, STX6, EIF2AK3, and MOBP [3,4]. Significant disease association with education level, years of exposure to well-water and to metals, and stress

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levels have also been reported [5–7].

Prior studies have evaluated the association of other risk factors including hypertension with PSP, but the findings remain controversial [8,9]. In 1997, Ghika et al. hypothesized that pre-symptomatic hypertension was a risk factor for PSP believing that adrenergic nuclei in the brain stem were affected by neurodegeneration and identified that 81% of the study's 42 living PSP patients had hypertension [10]. Similar findings were noted in Papapetropoulus et al.'s study who identified hypertension as a common co-morbid condition in PSP patients [11]. However, other studies had conflicting results and were unable to replicate these findings [12–15]. Moreover, PSP was defined inconsistently in these studies evaluating hypertension (either clinically or pathologically), therefore, making it difficult to compare findings between studies. Additionally, none of these studies accounted for the lag-time that exists between the neurodegenerative disease onset and the symptomatic presentation [5]. Therefore, it remains unclear whether hypertension was being evaluated as an associated disease symptom or risk factor in many of these studies. Although the lag-time in PSP is at present unclear, a study design that identifies hypertension with a 10-year lag time would provide stronger evidence for risk factor identification. The present study addresses limitations of previously published work by providing a large sample size, age-, sex-, race-matched controls, study population heterogeneity, disease lag-time, and unbiased inclusion/exclusion criteria. Additionally, we evaluated disease association with comorbid vascular conditions and classes of anti-hypertensive medications.

2. Methods

The methods of the study have been discussed in detail in prior published work [5,16]. In summary, between 2006 and 2013, patients with PSP and healthy controls without neurodegenerative disease were recruited from 15 centers across North America. Eligibility was defined as a PSP diagnosis in the past year based on National Institute of Neurological Disorders and Stroke-Society for PSP (NINDS-SPSP) criteria. Clinical diagnosis was determined by the screening site principal investigator. Cases with dementia or cognitive impairment were excluded using a Mini-Mental Status Examination (MMSE) score of ≤ 24. Additionally, cases with other nervous system pathology were excluded. MRIs were done when clinically indicated in patients with history of TIAs, strokes, or vascular risk factors. Patients with MRIs with ischemic lesions were excluded. Controls were individuals that cases identified as an age- and sex- matched, non-blood relative. The Telephone Interview of Cognitive Status (TICS-M, with score 27) and Telephone Questionnaire for Parkinson disease (PD) were used to exclude dementia and parkinsonism in the controls [17,18].

From a total of 280 controls and 280 cases with PSP, 277 healthy controls and 277 cases were included in the analysis. Three case-control pairs that identified a history of hypertension but listed a non-anti-hypertensive medication such as “Black Cahosh” were excluded from the analysis. From a telephone interview, cases and controls were asked about their medical history and medications. Cases and controls were defined as having hypertension if they had a self-reported medical history of hypertension (10 years prior to PSP symptom onset) and were taking an anti-hypertensive medication primarily for this medical problem (for at least 6 months since the age of 30). Some study subjects listed “unknown” for their anti-hypertensive medication and analyses were completed with including and excluding these five case-control pairs. The IRB approved the use of human subjects in this study. Written informed consent was obtained from all participants.

2.1. Statistical analysis

SPSS V.23 and Microsoft Excel were used for statistical analysis. Descriptive analyses were performed to compare the distribution of demographic variables among cases and controls using frequencies (percentages) and means. The $\chi 2$ statistic was used to compare proportions for categorical variables (e.g. race, sex, etc.). Comparison of means was performed using the ANOVA statistic. Study subjects with missing data for demographic characteristics were dropped from the demographic analysis, which was a rare occurrence.

Conditional logistic regression model analysis was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for the association between predictor variables and disease. A univariate conditional logistic regression model was first completed to adjust for possible confounders and then a multivariate conditional logistic regression analysis was completed only with predictor variables with a p-value < 0.05. The univariate analyses calculated odds ratios for the following predictor variables: education level, hypertension, hypertension related conditions (diabetes mellitus and hyperlipidemia), and classes of anti-hypertensive medications.

Table 1
Demographics of the study population.

	Cases	Controls	*p-value*
	N = 277	N = 277	
General Demographics			
Age	68.87 ± 6.913	69.02 ± 7.365	0.807
Sex			
Male	137 (0.49)	137 (0.49)	1
Female	140 (0.51)	140 (0.51)	1
Ethnic Group			
Asian or Pacific Islander	5 (0.02)	5 (0.02)	1
Black or African American	1 (0.003)	1 (0.003)	1
White or European American	271 (0.98)	271 (0.98)	1
Race			
Caucasian	271 (0.98)	271 (0.98)	1
Non-Caucasian	6 (0.02)	6 (0.02)	1
Education Level			
Grade School (grades 1–8)	5 (0.02)	4 (0.01)	0.737
High School (grades 9–12)	36 (0.13)	23 (0.08)	0.073
High School Diploma	75 (0.27)	49 (0.18)	**0.008**
Trade or Technical School	2 (0.01)	0 (0.0)	0.157
College Diploma	84 (0.30)	81 (0.29)	0.780
Graduate School Diploma	75 (0.27)	120 (0.43)	< **0.001**
Neurological Examination			
Total PSP Score	36.51 ± 11.129		
Total UPDRS	51.93 ± 17.865		
Total MMSE	27.36 ± 2.061		
Total DRS	126.86 ± 10.629		
Disease Duration	3.70 ± 1.768		
Total FAB scoring	13.23 ± 2.995		
FAB z-score reported	−2.59 ± 3.160		
FAB z-score central site	−2.58 ± 3.172		

N = number, m = %. DRS = Dementia Rating Scale (range 0–144), FAB = Frontal Assessment Battery (range 0–18), UPDRS = Unified Parkinson Dementia Rating Scale. The following number (%) of cases had missing scores for their neurological examination: Total PSP Score: 1(0.004); Total UPDRS Score: 1(0.004); Total DRS Score 1(0.004); Disease Duration: 1(0.004); FAB z-score reported: 3(0.011); FAB z-score central site: 3(0.011).

3. Results

3.1. Demographics

Table 1 summarizes the demographic and clinical characteristics. There was no difference (p-value = 0.807) seen in the mean age between the cases (68.9 ± 6.9) and controls (69 ± 7.4). Overall, there were more females (51%) than males (49%) in the study population. Education level was significantly different between the cases and the controls in the high school diploma (p-value = 0.008) and graduate

Table 2
Conditional regression analysis for predictor variables.

Univariate Model				
Predictor Variable	OR	Lower 95% CI	Upper 95% CI	p-value
Education Level	0.733	0.637	0.843	< **0.001**
HTN	1.569	1.129	2.181	**0.007**
HLD	1.077	0.768	1.509	0.667
DM	1.103	0.668	1.824	0.701
ACEI/ARB	1.500	0.984	2.287	0.060
Beta Blocker	2.000	1.053	3.799	**0.034**
Calcium Channel Blocker	1.357	0.833	2.211	0.220
Diuretic	0.844	0.506	1.408	0.516
Other	0.800	0.215	2.979	0.739
Multivariate Model				
Predictor Variable	OR	Lower 95% CI	Upper 95% CI	p-value
Education Level	0.730	0.633	0.841	< **0.001**
HTN	1.492	1.045	2.129	**0.027**
Beta Blocker	1.643	0.824	3.274	0.158

Significant associations noted between PSP and hypertension and education level in the multivariate model. HTN: hypertension. HLD: hyperlipidemia. DM: diabetes mellitus. ACEI/ARB: ACE-inhibitor/angiotensin receptor blocker.

diploma (p-value < 0.001) categories. The case group had a greater prevalence of high school diplomas and the control group had a greater prevalence of graduate school diplomas.

3.2. Associations with PSP

Table 2 summarizes the results of the univariate and multivariate conditional regression models for all predictor variables. In the univariate model, there were significant associations seen between PSP and hypertension (OR: 1.569; 95% CI 1.129–2.181; p-value = 0.007), education level (OR: 0.733; 95% CI 0.637–0.843; p-value < 0.001) and beta-blocker use (OR: 2.000; 95% CI 1.053–3.799; p-value = 0.034). However, in the multi-variate analysis hypertension (OR: 1.492; 95% CI 1.045–2.129; p-value = 0.027) and education level (OR: 0.730; 95% CI 0.633–0.841; p-value < 0.001) were the only significant associations. Results remained consistent even after excluding the five case-control pairs that had listed an unknown anti-hypertensive medication in their medication history.

3.3. Hypertension and anti-hypertensive use

Table 3 summarizes the number of subjects with hypertension and the type of anti-hypertensive medication they utilized, 45% of the control group and 57% of the case group had hypertension.

4. Discussion

This study not only sought to examine the controversial association of hypertension with PSP, but also other disease associations that have been linked to other tauopathies such as anti-hypertensive medications, diabetes, and hyperlipidemia. Although there has been limited data in PSP models of disease, data from other tau-mediated diseases like Alzheimer disease (AD) may provide insight into PSP disease pathology and associated risk.

4.1. Hypertension

This study shows that the presence of hypertension preceding at least 10 years of onset of PSP symptoms is approximately 1.5 times more common in clinically diagnosed PSP cases than in healthy controls. This association is significant in both univariate and multivariate models. Of note, the history of hypertension verified by anti-hypertensive use and the 10-year lag time provide temporal separation between hypertension and PSP onset, removing ambiguity of both diseases co-occurring. Earlier hypotheses suggested that hypertension may play a role in the development of cerebrovascular disease that leads to selective microinfarcts in PSP specific neuronal structures, despite that no infarcts are seen on neuropathology. However, vascular PSP is rare and ischemia has not been identified as a central cause of the disease process [19]. Rather, it is more likely that hypertension potentiates the development of PSP instead of acting as a central mechanism. Using AD and tau mouse models, Diaz-Ruiz et al. demonstrated that chronic hypertension may lead to beta-amyloid and tau-protein aggregation and suggested based in their study that it could increase the progression of AD and other tauopathies like PSP [20]. Furthermore, neuroinflammation has been linked to PSP development and hypertension is well-known to be associated with inflammatory mediators [21,22].

4.2. Anti-hypertensive medications

If hypertension is associated with an increased risk of PSP, then it is reasonable to hypothesize that anti-hypertensive use may be considered protective. However, our study found that beta-blocker use for hypertension may be associated with an increased risk for developing PSP. The effect of beta-blockers on tau pathology in AD mouse models is controversial and data has varied in many studies. Some evidence supports that beta-adrenergic blockade improves phosphorylation of tau proteins and cognitive deficits whereas others show that it worsens this pathology [23,24]. The literature has described anti-hypertensive treatment to be associated with a decreased risk of AD in epidemiological studies [25,26]. In mouse models, based on the renin-angiotensin hypothesis for AD, angiotensin converting enzyme inhibitors and angiotensin receptor blockers have been associated with decreasing tau pathology [27].

4.3. Diabetes and hyperlipidemia

We examined hypertension related co-morbidities since these diseases are known to promote vascular pathology in addition to increasing oxidative stress and inflammation which may associate to neurodegeneration [28]. Specifically, both hyperglycemia and hypercholesterolemia have been shown to increase tau pathology in AD mouse models as well [29,30]. Although not statistically significant, our results showed that diabetes mellitus and hyperlipidemia have a positive trend with PSP.

4.4. Education level

Higher education level has been shown to be negatively associated with PSP in prior studies and in our multiple regression analysis [5,16].

Table 3
Frequency anti-hypertensive medication use.

Subjects with Hypertension	Total	ACEI/ARB	Beta Blocker	Calcium Channel Blocker	Diuretic	Other
Cases	158 (0.57)	61	30	42	29	4
Controls	125 (0.45)	43	16	32	34	5

57% of all cases and 45% of all controls at hypertension. Percentages are not provided for each anti-hypertensive medication category since patients may have been taking more than one type of medication.

Results from our study are in agreement with this finding in PSP. Low education has also been reported to be associated with other tau disorders such as AD [26].

4.5. Strengths and limitations

Major study strengths include large sample size and accounting for disease lag-time which were not present in prior studies examining the association between PSP and hypertension [10–14]. Incorporation of lag time is a common way to try to differentiate early symptomatology from causal factors. A minimum of 10 years was considered appropriate to identify associations that were potentially causative. On the other hand, it could be argued that hypertension could be a prodromal feature of PSP. However, while the prodromal features of PD persist during the manifest disease, hypertension is not a common PSP feature. Therefore, this possibility is unlikely.

Limitations of this study include using a clinical rather than pathological diagnosis of PSP and recall bias. However, the diagnosis of PSP is quite accurate when using the NINDS-SPSP criteria and the site investigators were experts in the field. The clinical diagnosis of probable PSP meeting the NINDS-SPSP criteria has a high specificity (98%) and positive predictive value (100%). The criteria include presence of vertical supranuclear gaze palsy and postural instability with unexplained falls within the first year of symptom onset without neuroradiologic evidence of relevant structural abnormality except for atrophy [2]. The diagnosis of hypertension was based on what cases and controls reported as a part of their medical history and when available what was documented in their medical records. However, a blood pressure reading at the time of contact for the study would not necessarily provide evidence of hypertension if subjects were taking anti-hypertensive medication. Additionally, a pilot study comparing the responses of PSP patients with their medical records showed that patients' responses were accurate (data not presented). Recall bias was limited by the exclusion of dementia and cognition screening tests during study enrollment. Moreover, there are no reasons for cases to report more frequently a history of hypertension receiving treatment when they were unaware of our hypotheses.

It would have been ideal to have MRIs of all patients but in view of cost, neuroimaging was not used in the study as an assessment to exclude individuals with history of microangiopathy or other neurological vasculopathies. However, having stroke lesions in PSP affected areas was a study exclusionary criterion. It could be argued that we should adjust for all the other risk factors of the main study. However, this is one of the three aims of our NIH project. Given the distinct nature of the three primary aims we feel it is justified to treat them separately and not adjust for multiple comparisons including all analyses from the parent study. This is a very common approach taken by many major epidemiological studies whose data are analyzed over time to address very distinct hypotheses. Moreover, hypertension is unrelated to our two other study hypotheses that included determining whether exposure to environmental factors such as pesticides/metals/etc. could lead to oxidative or possible protective factors such as inflammation and statins.

5. Conclusion

Hypertension is a complex disease which is influenced by many vascular mediators that have been shown to play a role in tau pathology [20,27]. Although we can extrapolate from other tauopathies, more studies are needed to elucidate which anti-hypertensives are detrimental versus beneficial in tau pathology specifically in PSP mouse models. Nevertheless, our present study does confirm that hypertension is associated with PSP and precedes its development. Strategies for disease prevention using this new clinical risk factor should be particularly considered when biological markers will allow to identify patients at risk for PSP.

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