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The Role of Stress as a Risk Factor for Progressive Supranuclear Palsy

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Running Title: The Role of Stress as a Risk Factor for PSP

ABSTRACT:

Background: PSP, like Alzheimer's disease (AD), is a tauopathy. The etiopathogenesis of PSP is not well known and the role of stress has not yet been examined. Recent studies have shown that stress increases the risk for developing AD. This study investigates the role of stress as a risk factor for PSP.

Objective: To examine the association between the development of progressive supranuclear palsy (PSP) and self-reported life stressors.

Methods: 76 patients diagnosed with PSP according to the NINDS-SPSP criteria and 68 age-matched unrelated controls were administered a life stressor questionnaire. Stress was quantified as total number of events, number of life changing events, and number of events characterized by self-rated severity. Conditional odds ratio (OR) was calculated for each measure, with participants in the highest quartile of each measure being defined as high-exposure in relation to all other participants.

Results: There were no significant differences between the reported number of total events or life-changing events in cases and controls. However, we found 24.4% of cases (N=11) and 9.1% of controls (N=5) were defined as experiencing high exposure to high severity events, yielding an OR of 3.2 (p=0.04).

Conclusions: We found that cases have over a three times greater odds of high exposure to high-severity events than controls while there were no differences in overall number of reported events. Our findings suggest that high exposure to highly stressful events may be associated with the development of PSP.

Key Words: Progressive supranuclear palsy (PSP), stress, epidemiology, case-control

INTRODUCTION:

The etiology of PSP is currently unknown, however, it is believed that genetic, environmental, oxidative, and inflammatory factors may all contribute[1, 2]. **A recent genome-wide association study identified a genetic risk factor, MAPT, which is comparable to the risk associated with the APOE ε3/ε4 genotype for AD[2].** In recent years there have been numerous studies examining the role of stress in the etiology of diverse medical conditions[3-7]. Thus far, the role of stress as a potential risk factor for PSP has not been studied.

Stress has been shown to have a role in the development of Alzheimer's Disease (AD). Studies have demonstrated that prolonged exposure to psychological stressors in older non-demented individuals with the presence of a known genetic risk factor, leads to accelerated memory decline[8]. An association between stress and the pathogenesis of AD has also been demonstrated in mouse models, in which AD transgenic mice exposed to glucocorticoids, the hormonal response to stress, increase tau accumulation and therefore, demonstrate accelerated development of neurofibrillary tangles[9]. **Additionally, in a study involving healthy, wild-type mice, it was shown that the experience of chronic stress and increased glucocorticoid release induced hyperphosphorylation of tau[10]. This supports the hypothesis that even in individuals without genetic risk factors, chronic stress may be a risk factor for developing a tauopathy.**

Pathologically, PSP is one of the "tauopathies", a series of diseases in which tau is hyperphosphorylated and aggregates to form neurofibrillary tangles and tufted astrocytes[11]. AD is the most common tauopathy[12].

Given that both pathologic similarities between PSP and AD, in light of the findings implicating stress in the development of AD and in other disorders, this study investigated the role of stress as a risk factor for PSP. Based on the literature review and our clinical practice, we hypothesized that PSP patients would report a greater number of high severity life stressors when compared to controls.

MATERIALS AND METHODS:

Participants:

PSP patients (i.e. cases) were recruited from 9 enrollment sites: (Baylor University, University of Colorado, Case Western Reserve, Emory University, University of Louisville, University of Alabama Birmingham, University of California at Los Angeles, Mayo Clinic Jacksonville, and University of Maryland). Internal Review Board approval was obtained at each participating site. All participants completed a consent form for enrollment in this study. The final sample consisted of 143 participants (76 cases, 68 controls).

The majority of PSP patients met the National Institute of Neurological Disorder and Stroke Society for PSP Inc. (NINDS-SPSP) criteria for clinically probable or definite PSP, the remaining 10% of the patients (N=8) met criteria for clinically possible PSP[13].The majority of enrolled patients scored >24 on the Mini Mental Status Examination (MMSE)[14]. An exception of the MMSE cutoff was made for 5 participants, who the primary site PI did not believe met the clinical criteria of cognitive impairment. Potential participants with other central nervous system disorders were excluded. PSP patients were asked to identify an age (+/- 5 years) and gender matched non-blood related control. Spouses were not included. Controls were screened for dementia using the Telephone Interview for Cognitive Status (TICS)[15] and were also screened via telephone interview for parkinsonism.

Measures:

Life Stressors Questionnaire: All participants were administered a life stressor questionnaire by trained study personnel. The major life events in this study were derived from a 61-item questionnaire developed by Paykel[16]. Some of the events from the original questionnaire were omitted from the study (n= 25 events) because they were outdated or uncommon (e.g., child going off to war) **or they were not thought to represent an event that would cause "prolonged stress" ("take an important exam" or "academic failure"). Prolonged stress is defined as lasting for two weeks or longer[8]**. Some life events were combined into a single event (e.g. "move within the same city" was combined with "move to a new city within the same country"). Moreover, additional relevant questions (n=6) were added to the questionnaire from other life event questionnaires to make up the full questionnaire used in this study[17, 18]. The final version of the questionnaire had a total of 36 questions and is available in the supplemental materials. Participants were asked for each event they experienced to rate the stress impact as low, mild, or high, to state whether this was a life-changing event, and to report the specific year the event occurred.

All reported events were recorded; however, only events reported as occurring prior to the "reference year" were included in the statistical analyses. The reference year for each case, and associated control, was defined as 10 years prior to the date of first reported PSP symptom. The purpose of this time frame is to account for the hypothesized lag time for PSP to manifest clinically. Though there is no published literature on the length of this lag time, we chose 10 years to be on the conservative side to avoid including possible preclinical and prodromal disease periods.

Quantification of Measure: Data from the life stressors questionnaire were quantified for each participant as follows: 1) total number of events, 2) number of life-changing events, and 3) total number of events self-rated as "high severity".

Statistical Analysis: Data were assessed for normal distribution graphically using QQ plots. All tests of significance were two-tailed and alpha was 0.05. Statistical analysis was performed using "R", and the packages "gmodels", "epitools", and "car".

Demographic Data: For continuous variables the mean and standard deviation are reported for cases and controls; differences were assessed using the Student's t-test. For categorical variables, frequencies and proportions are reported for cases and controls; differences were assessed using Fisher's exact test.

Life Stressors Data: For each of the different measures of the life stressor questionnaire, mean and standard deviation was determined for cases and controls. The measures of life stressors were found to have a non-normal distribution. Differences between life stressors were assessed using the Wilcoxon-rank sum test.

Participants were classified into "life stressor exposure groups" for each method of life stressor quantification. To classify exposure level, the quartiles for each life stressor quantification method were determined. Participants who reported a greater number of events than the cut-off between the third and fourth quartile of the measure, were classified as having experienced "high exposure". Participants who reported a less than or equal to number of events as the cut-off between the third and fourth quartile were defined as having experienced "normal exposure". Conditional odds ratios (OR) with 95% confidence intervals were calculated. Significance for unadjusted ORs was assessed using Chi-Square test.

Adjusted ORs for high exposure to each measure were determined by performing logistic regression controlling for age and gender. The adjusted ORs are reported with 95% confidence intervals. Significance for adjusted ORs was determined using Chi-Square test.

Cognitive Functioning and Life Stressor Quantification Methods:

In order to assess if cognitive function in participants affected scores in the various methods of life stressor quantification, correlation testing between measures of cognitive function and life stressor quantification scores was performed. Measures of cognitive function in cases were: Dementia Rating Scale (DRS) [19], Frontal Assessment Battery (FAB)[20], and MMSE[14]. The measure of cognitive function in controls was the TICS[15]. Pearson's correlation coefficient and p-value were reported.

RESULTS:

Demographics: Demographic data for the 76 cases and 67 controls are presented in Table 1. There were no significant between-group differences in baseline demographics. There was an expected statistically significant difference between cases and controls current level of independence.

Life Stressors Data: Table 2 shows there was no between-group statistically significant differences in number of reported total events (cases: 5.4, controls: 5.5), and life-changing events (cases: 2.9, controls: 3.1). Similarly, there was no difference when participants were categorized based on exposure to either of these measures. Additionally, no differences existed when adjusting for age and gender for either of these measures.

There was no statistical between-group difference in the number of self-reported highly stressful events (cases: 3.4, controls: 2.6). However, there was a statistical difference when participants were categorized based on exposure level, 24.4% of cases (N=11) and 9.1% of controls (N=5) were defined as high exposure, yielding an estimated OR of 3.2 (p=0.04). When adjusting for age and gender the cases remained at increased odds of high exposure to total number of highly stressful events with an adjusted OR of 3.4 (p=0.04).

Correlation of Cognitive Measures and Life Stressor Measures:

There was no significant correlation between the DRS, FAB, MMSE, or TICS and any of the life stressor quantification methods. Results are presented in Table 3.

DISCUSSION:

We used a case-control study design to examine the potential role of stress as a risk factor for PSP. We hypothesized that the experience of high levels of stress prior to the onset of disease would occur more often in the cases than controls. Our hypothesis was based on the fact that: (1) in vivo studies show that glucocorticoids, hormones released in response to stress, accelerate the development of neurofibrillary tangles[9]; (2) stress has a role in AD, a related tauopathy[8]; and (3) in our practice many PSP patients report stress preceding the onset of their symptoms.

We found that (1) there was no significant difference between the total number of events reported by cases and controls; however, as predicted (2) there was a significant association between high exposure to high-severity life stressors and PSP. PSP patients were found to be three times more likely to report high exposure to highly stressful events than controls. This suggests that these highly stressful events may have a role in the etiopathogenesis of PSP.

Future studies should address the role of highly stressful events in the development of PSP to clarify this relationship.

This study has several limitations. One limitation is that, like many retrospective surveys, there is concern that as events may have occurred years earlier the events may not be recalled accurately. Due to the possible effect of PSP on memory, the exclusion criteria for cases was an MMSE score of less than 24, which is the established cut-off for dementia. To further address concerns about mental status influencing recall bias, we performed correlation analyses and found no significant correlations between various measures of cognitive functioning and the life stressor variables. Finally, it is possible that the significance found in our study is due to multiple comparisons.

A major strength of this study is that it is the first study to investigate the role of experienced life stress as a risk factor for PSP. Given the severity of PSP, and the unfortunate lack of therapeutic intervention, it is important to improve our understanding of the pathogenesis and risk factors for this disease. By better understanding the potential role of high exposure to highly stressful events, we can emphasize the importance of stress management in individuals at risk of developing disease once accurate biological markers of PSP are identified. An additional strength of the study is that we incorporated the concept of "lag time", the hypothesized time it takes for PSP to manifest clinically after development. Other studies investigating stress as a risk factor for disease have also incorporated "lag time"[4, 5, 7]. This serves to minimize the reporting of events that occurred as a result of the presence of disease, and additionally, leads to only events that occurred at a biologically plausible time to be analyzed as potential risk factors for PSP. Finally, an additional strength of this study is that a relatively large number of patients were recruited for a rare disease. Our study included comparable numbers of cases

and controls, as do numerous other similar studies investigating the role of stress in the etiopathogenesis of disease[3-5].

In summary, our study found a significant association between high exposure to high severity life stressors and PSP. As this study is the first to investigate this potential risk factor, further investigations are needed to better understand this relationship. Future studies should focus specifically on these highly stressful events, as these appear to be the most significant in their association with PSP. **Additionally, we hope that future studies will be able to investigate for a potential interaction between the recently discovered genetic risk factor for PSP, MAPT, and the occurrence of life stressors. This is of particular interest as in many of the AD studies the most significant relationship between experienced stress and occurrence of AD was found in those with identified genetic risk factors.** Finally, it would be important as well to determine whether highly stressful events may accelerate the progression of symptoms associated with PSP.

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COMPETING INTERESTS:

Dr. Litvan is also an investigator in studies funded by 5P50 AG005131-31, 5T35HL007491, 1U01NS086659, 1U54NS092089-01, Parkinson Study Group, Michael J Fox Foundation, CBD Solutions-CurePSP, AVID Pharmaceuticals, C2N Diagnostics and Bristol-Myers and Squibb. She receives her salary from the University of California San Diego. She was member of the Pfizer, Abbvie Northera and Bristol-Myers and Squibb Advisories Boards. Dr. Riley has received honoraria from Allergan, Lundbeck and Teva. Dr. Bordelon received speaker honoraria from Teva and Lundbeck. Dr. Standaert is also an investigator in studies funded by Abbvie Laboratories, the American Parkinson Disease Association, the Bachmann-Strauss Foundation, the Dystonia Medical Research Foundation, Acerta Pharmaceuticals, Ceregen, Inc, The MGH XDP Consortium, the Michael J. Fox Foundation for Parkinson Research, and NIH grants P20NS092530, K23NS080912, R25NS079188, K01NS069614, 1F31NS084722, 1F31NS084722, F31NS081963, R01NS064934 and P50NS037409. In addition, in the last three years he has served as a consultant for or received honoraria from Auspex Inc., Teva Neurosciences, Serina Therapeutics, Lundbeck, Abbvie, Bradley Arrant Boult Cummings, Banner Sun Health, Viropharma (now Shire), and he has received royalties for publications from McGraw Hill, Inc. Dr. Reich received research funding from NIH-NINDS/ORDR-NCATS. He received royalties from Informa and from being a reviewer of UpToDate.

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TABLES:

Table 1: Demographics of Cases and Controls

	Case	Control	Significance
Number of Subjects	76	68	
Current Age:			p = 0.88
Mean ± Standard Deviation (SD)	68.1 ± 6.8	67.9 ± 6.6	
Years Since First Reported Symptom:			NA
Mean ± Standard Deviation (SD)	4.1 ± 3.9	NA	
Gender:			p = 0.74
Males: Percent (N)	53.9% (41)	50.0% (34)	
Females: Percent (N)	46.1% (35)	50.0% (34)	
Marital Status at Reference Year:			p = 0.31
Married: Percent (N)	94.7% (72)	88.2% (60)	
Divorced: Percent (N)	1.3% (1)	7.4% (5)	
Never Married: Percent (N)	2.6% (2)	2.9% (2)	
Widowed: Percent (N)	1.3% (1)	1.5% (1)	
Annual Income at Reference Year:			p = 0.45
$5,000- $29,999 (N)	3.9% (3)	6.0% (4)	
$30,000 - $59,999 (N)	32.9% (25)	34.3% (23)	
$60,000+ (N)	51.3% (39)	55.2% (37)	
Did Not Report (N)	11.8% (9)	4.5% (3)	
Highest Level of Education:			p = 0.54
Grade School: Percent (N)	3.9% (3)	1.5% (1)	
High School: Percent (N)	18.4% (14)	23.5% (16)	
High School Diploma: Percent (N)	18.4% (14)	14.7% (10)	
College Diploma: Percent (N)	23.7% (18)	32.4% (22)	
Graduate School Diploma: Percent (N)	32.9% (25)	27.9% (19)	
Technical or Trade School Diploma: Percent (N)	2.6% (2)	0.0% (0)	
Years of Schooling Prior to Reference Year:			p = 0.51
Mean SD	15.2 ± 3.1	15.6 ± 3.7	
Ethnicity:			p = 0.78
White or European-American: Percent (N)	93.4% (71)	95.6% (65)	
Black or African American: Percent (N)	1.3% (1)	1.5% (1)	
Asian or Pacific Islander: Percent (N)	2.6% (2)	2.9% (2)	
Latino/Latina or Hispanic: Percent (N)	2.6% (2)	0.0% (0)	
Employment Status at Reference Year:			p = 0.76
Full-Time Employed: Percent (N)	65.8% (50)	76.5% (52)	
Part-Time Employed: Percent (N)	10.5% (8)	5.9% (4)	
Retired: Percent (N)	18.4% (14)	14.7% (10)	
Homemaker: Percent (N)	2.6% (2)	1.5% (1)	
Unemployed: Percent (N)	1.3% (1)	1.5% (1)	
Disabled: Percent (N)	1.3% (1)	0.0% (0)	
Current Living Situation:			p = 0.38
Lives with Spouse or Partner: Percent (N)	88.2% (67)	85.3% (58)	

Lives with Friend or Relative: Percent (N)	5.3% (4)	2.9% (2)	
Lives Alone: Percent (N)	5.3% (4)	11.8% (8)	
Lives with Group: Percent (N)	1.3% (1)	0.0% (0)	
Current Type of Residence:			p = 0.31
Single Family Residence: Percent (N)	90.8% (69)	94.1% (64)	
Apartment: Percent (N)	1.3% (1)	1.5% (1)	
Condo: Percent (N)	0.0% (0)	3.0% (2)	
Retirement Community: Percent (N)	1.3% (1)	1.5% (1)	
Assisted Living Facility: Percent (N)	2.6% (2)	0.0% (0)	
Skilled Nursing Facility/Nursing Home: Percent (N)	3.9% (3)	0.0% (0)	
Current Level of Independence:			p < 0.001
Lives Independently: Percent (N)	44.7% (34)	98.5% (67)	
Requires Some Assistance with Complex Activities: Percent (N)	25.0% (19)	0.0% (0)	
Requires Some Assistance with Basic Activities: Percent (N)	30.3% (23)	1.5% (1)	
Dementia Screening Tools:			
Cases – MMSE: Mean ± SD	27.7 ± 2.1	N/A	
Controls – TICS: Mean ± SD	N/A	38.4 ± 4.2	

Table 2: Life Stressor Quantification Methods Results

	Cases: Mean ± SD	Controls: Mean ± SD	p-value	High Exposure Cut-Off**	Cases High Exposure: Percent (N)	Controls High Exposure: Percent (N)	Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Total Number of Events	5.4 ± 3.9	5.5 ± 2.8	0.25	7	25.3% (19)	17.7% (12)	1.6 (0.7 – 3.6)	0.27	1.6 (0.7 – 3.6)	0.28
Total Number of Life-Changing Events	2.9 ± 2.9	3.1 ± 2.1	0.09	4	16.7% (11)	18.8% (12)	0.9 (0.3 – 2.2)	0.76	0.9 (0.4 – 2.4)	0.76
Total Number of High Stress Events	3.4 ± 3.2	2.6 ± 1.6	0.37	4	24.4% (11)	9.1% (5)	3.2 (1.0 – 11.0)	0.04	3.4 (1.1– 11.7)	0.04

**Participants with values greater than this cut-off are defined as having experienced high exposure. Participants with values less than or equal to this cut-off are defined as having experienced normal exposure.

Table 3: Cognitive Functioning and Life Stress Quantification Methods - Pearson's Correlation Coefficient (r)

	Cases: MMSE r (p-value)	Cases: DRS r (p-value)	Cases: FAB r (p-value)	Controls: TICS r (p-value)
Total Number of Events	0.05 (0.68)	-0.01 (0.95)	0.02 (0.88)	0.16 (0.20)
Total Number of Life Changing Events	0.04 (0.74)	0.04 (0.73)	0.09 (0.50)	0.13 (0.30)
Total Number of High Stress Events	0.07 (0.63)	0.07 (0.64)	0.07 (.62)	0.23 (0.09)

Supplemental Material

Table1: Life Stressors Questionnaire

Life Event
Became a primary caregiver
Began an extramarital affair [1]
Business failure [1, 2]
Change in line of work [1, 3]
Change in work condition [1, 2, 3]
Child enters the armed services [1, 2]
Child leaves home [1, 3]
Child married [1]
Death of a child [1]
Death of a close family member [1]
Death of a close friend [1, 3]
Death of a spouse [1, 2, 3]
Demotion [1, 2]
Divorce [1, 2, 3]
Fired [1, 2, 3]
Hospitalization of a family member [1]
Involved in a serious accident [2]
Jail sentence/imprisonment [1, 2, 3]
Lawsuit [1, 2]
Loss of driver's license [2]
Major change in living condition [3]
Major change in health or behavior of a family member [3]
Major financial difficulties [1, 2, 3]
Major personal physical illness [1, 2, 3]
Marital separation [1, 2, 3]
Marriage [1, 2, 3]
Menopause [1]
Miscarriage or stillbirth [1]
Move to another country [1]
Move within the United States [1]
New person in household [1, 2]
Promotion [1, 2]
Retirement [1, 2]
Sexual difficulties [3]
Spouse unfaithful [1]
Unemployed for one month [1,2]
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