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Disease-related and genetic correlates of psychotic symptoms in Parkinson's disease

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Abstract

Objective—To examine disease-related and genetic correlates of the development of psychotic symptoms in a large Parkinson's Disease (PD) population.

Methods—We studied 500 PD subjects from the NeuroGenetics Research Consortium using logistic regression models. Predictors were demographic, clinical (motor/ non-motor features) and genetic measured as continuous or dichotomous variables. Continuous measures were divided into population based tertiles.

Results—Results are given as odds ratios (95% confidence intervals) for dichotomous variables and by ascending tertile for continuous variables. Psychotic symptoms were associated with increasing age; 4.86 (1.62-14.30), and 6.25 (2.09-18.74) (test for trend p=.01); and duration of disease 3.81 (1.23-11.76), and 5.33 (1.68-16.89) (test for trend p=.03). For non-motor features we

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demonstrated positive trends with depression, 1.31 (0.47-3.61), and 5.01 (2.04-12.33) (test for trend p<.0001) and cognitive dysfunction, 0.69 (0.26-1.84) and 2.51 (1.00-6.29) (test for trend p=.03), and an excess for those with sleep disorders, 2.00 (1.03-3.89) (p=.04). Psychotic symptoms were not associated with tremor or postural instability scores but there was an association with freezing of gait, 3.83 (1.67-8.75) (p<.002). Psychotic symptoms were not associated with the presence of any examined polymorphisms in the apolipoprotein, alpha-synuclein, or *MAPT* genes.

Conclusion—This is the largest study to examine correlates of psychotic symptoms in PD. We discovered a novel association with freezing of gait. We demonstrated an association with depression and duration of disease, both of which were inconsistently related in prior studies, and confirmed the association with age, cognitive dysfunction and sleep disorders.

Keywords

Parkinson's disease; psychosis; depression; sleep; freezing of gait; genetics; risk factors

Introduction

Psychotic symptoms (PS) including hallucinations and delusions, occur in as many as 60% of Parkinson's disease (PD) patients based on longitudinal studies[1, 2]. The consequences of their development are significant including nursing home placement and increased mortality[3, 4]. It has been well recognized that all anti-PD drugs in current use are capable of triggering PS and clinical trials have demonstrated this[5]. It was felt for a long time that these phenomena were primarily drug-induced and hence the terms “drug-induced psychosis” and “levodopa psychoses”[6, 7]. The paucity of data on psychosis from the pre-levodopa period supported this notion [8] but it is becoming increasingly clear that psychosis reflects a complex interaction between the underlying disease and its treatment[9]. There is now substantial data to suggest that medications are not the primary factor required for the development of PS in PD. First, hallucinations are a frequent symptom of dementia with Lewy bodies in the early stages prior to treatment of the parkinsonism with dopaminergic agents[10,11]. There have been some reports of hallucinations in untreated PD patients as well [9, 12, 13]. Also, not all patients treated with these drugs develop psychotic symptoms. There is no simple dose relationship and in comparing those patients with and without hallucinations there was no difference related to levodopa equivalent doses[9, 14]. Finally, a study switching hallucinating patients from oral to intravenous levodopa and pushing levels up did not result in a worsening of symptoms, in fact the symptoms cleared[15].

These results emphasize the importance of disease related and other factors. The objective of this study was to examine disease and genetic related correlates of the development of PS in a large population of PD patients by casting a wide net and examining demographic, motor, non-motor and genetic variables.

Methods

Subjects

This study was approved by the Institutional Review Boards of the participating institutions. Aspects of subject recruitment, data collection and molecular genetics have been reported

earlier [16] and will be summarized here. PD subjects were enrolled through the NeuroGenetics Research Consortium (NGRC) for a study of susceptibility genes in PD[17]. During single visits uniform and standardized methods were used across all sites for diagnosis, subject selection, and data acquisition (i.e. demographics, DNA extraction and genotyping). All patients met standard clinical diagnostic criteria for PD (modified UK brain bank criteria) [18] as determined by a movement disorder neurologist. Patients were enrolled sequentially, regardless of age at disease onset or family history of PD, and were unrelated to one another. Two NGRC sites, Emory University and Albany Medical Center, collected additional clinical data including the total UPDRS, MMSE and Beck Depression Inventory 2 (BDI2) and subjects from these sites were included in this analysis.

Molecular genetics

For this analysis, we selected genetic polymorphisms based on prior findings of impact on the risk of developing PD; *MAPT* (microtubule associated protein tau), *SNCA*-REP1 (α-synuclein promoter), and *APOE* (apolipoprotein E) [19].

MAPT—H1 haplotype is recessive with respect to PD risk [20]. Thus H2 heterozygotes and homozygotes were combined into one group designated as H2X and compared to H1H1. H1H1 was set as reference. To distinguish H1 and H2 haplotypes, a single H1-H2 SNP (*rs1800547*) that differentiates the two haplotypes was genotyped, using a TaqMan assay on an ABI 7900HT Sequence Detection System (Applied Biosystems) [20].

***SNCA* REP1—**Subjects carrying the genotype of the shorter 257 allele are at reduced risk, 259 homozygous (mid-size allele) is neutral, and subjects carrying the longer 261 allele are at increased risk of PD. Three genotypic classes were defined: 257X where X is 257 or 259, 261X where X is 261 or 259, and 259 homozygous. 257-261 heterozygous was excluded because the alleles have opposing effects on PD risk. The 259 homozygous group was set as reference. *SNCA* REP1 was PCR-amplified using fluorescently labeled primers,[21] and repeat length was determined by PCR using an ABI PRISM 3100 Genetic Analyzer and Genotyper version 3.7 software (Applied Biosystems, Foster City, CA) [22].

APOE—genotyping was carried out using a standard RFLP method and using a 3100 Genetic Analyzer and Genotyper software [23]. Four genotyping classes were defined: ε4 ε4, ε3 ε4, ε3 ε3 and ε2X (combing the rare ε2 ε2 with ε2 ε3 and excluding ε2 ε4 because ε2 and ε4 may have opposing effects on PD risk). ε3 ε3 was set as reference [20, 24, 25].

Statistical analysis

We performed a cross-sectional analysis to examine correlates related to the development of PS. The outcome was considered as a dichotomous variable and was defined from item 2 of the UPDRS referred to as thought disorder. This is a 0-4 scale where 0 = “normal”, 1 = “vivid dreams”, 2 = ““Benign” hallucinations with insight retained”, 3 = “Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities”, 4 = “Persistent hallucinations, delusions, or florid psychosis. Not able to care for self”. We considered a score of >1 to indicate the presence of PS and did not separate mild from

severe as mild often progress to more severe over time [26]. The 0 and 1 categories were combined as having no PS.

As correlates, we examined 13 demographic, clinical and genetic factors. Two of three demographic, two of four motor, and two of the three non-motor factors were continuous variables that were separated into tertiles based on the entire population. We did one analysis using tertiles for all continuous variables, and a second using these same variables as continuous variables as a test for linear trend. The rest of the variables were dichotomous.

The three demographic items were sex, age at diagnosis and duration of disease. Duration of disease was categorized into tertiles, the lowest (the referent group) was <=4.6 years, the middle tertile was 4.7-9.7 and the highest >9.7 years. For age at diagnosis the referent group consisted of the youngest tertile (age <=63.7), while the other groups were 63.8 to 72.9 and > 72.9. Categorical analysis of tertiles for age and duration avoids the assumption, inherent in using age and duration as continuous variables, that these variables have a strictly linear relationship with the odds of the outcome. Categorical analyses make no assumption about the nature of the relationship.

Motor risks included a tremor subscore, a composite of UPDRS part III (motor examination) items including number 20 (tremor at rest) scored for each limb and chin plus 21 (action or postural tremor of the hands). In total there were seven items summed, each scored 0-4, so that the sum had a maximum score of 28. Most items were scored 0, and the mean observed tremor subscore was 2.1, with a median of 2.0 and a standard deviation of 2.3. The tertiles were 0, 0.5-2.5, and >2.5. Gait/balance subscore (referred to as GBS), which was a composite of five items in the UPDRS part III, was also examined as a continuous variable. The items were numbers 27 (arising from a chair), 28 (posture), 29 (postural instability), 30 (gait), 31 (body bradykinesia and hypokinesia). All items were scored 0-4; maximum score of the sum was 20. The observed mean was 4.6, with a median of 4.0 and a standard deviation of 3.4. For GBS the categories were <=2.5, 3-5, and >5. Tremor subscore and GBS have been shown to have opposite effects on prognosis of PD [27]. We also examined freezing of gait (FOG) where we utilized UPDRS Part II item 14 (Freezing when walking), which was measured on a 0 - normal to 4 - severe scale and we dichotomized the score with > 1 being indicative of having freezing. For falling we used UPDRS Part II item 13 (Falling not caused by freezing), which was dichotomized in the same way.

Non-motor predictors were UPDRS item 41 (does the patient have a sleep disturbance, either hypersomnia or insomnia? 0 = yes, 1 = no), depression measured by the BDI2 as a continuous variable (maximum score 63) and cognition measured by the MMSE as a continuous variable (maximum score 30). The BDI2 and MMSE were categorized into tertiles as follows: BDI <=5, 5.5-10, and >10, MMSE categories were 30, 29-28, and <28.

Finally, we examined three dichotomous genetic predictors; *APOE* (ε4, ε2 alleles), REP1 (261 or 257 alleles) and *MAPT* (presence of H1H1).

We used a multivariate logistic model for our outcome. All 13 predictor variables were retained in the model rather than using any backward or forward selection procedure, as the number of correlates were limited, and some residual confounding might be expected from

variables selected out via a selection procedure set to a given arbitrary p-value. Variables with p<=0.05 were then highlighted for discussion and interpretation.

Results

Subjects included 500 PD cases; mean (+/- SD) age 67.7 (+/- 10.8) years, duration of disease 8.5 (+/- 6.2) years and 62% were men. Overall, 13% of subjects (63) had PS. The table shows data on frequency of all examined correlates, odds ratios (OR) and 95% CI. We found significantly associated factors in the following categories; demographic, motor, and non-motor but no genetic correlates found.

For demographic features correlation was increased with greater duration of disease. For 4.7-9.7 yrs vs. <4.6 yrs, the OR was 3.81 (95% CI 1.23-11.76, p=.02) and for >9.7 yrs vs. <4.6 yrs, the OR was 5.33 (95% CI 1.68-16.89, p<.005). The positive linear trend was significant (p=.03). Age differences between those with and without psychotic features were highly significant. With </= 63.7 yrs as the referent; from 63.8-72.9 years, the OR was 4.82 (95%CI 1.62-14.30, p=.005); for age >72.9 the OR was 6.25 (95% CI 2.09-18.74, p=.001). The linear trend was significant (p=.01).

For motor correlates PS were associated with the presence of FOG, OR 3.83 (95%CI 1.67-8.75, p<.002) but none of the other motor traits. For non-motor measures, depressive symptoms (BDI2), MMSE and sleep (presence of insomnia or hypersomnia) were significantly associated. For BDI2 the score of > 10 compared to the referent was significant OR 5.02 (95%CI 2.04-12.33, p<.0004), linear trend was also significant (p<.0001). For MMSE, the score of <28 compared to the referent was significant OR 2.51 (95% CI 1.00-6.29, p<.05), as was the linear trend (p=.03). For sleep OR 2.00 (95%CI 1.03-3.87, p=.04). Of genetic correlates, no evidence was found for an association with PS. The *SNCA*-REP 261 allele showed an increased risk which was borderline significant (p=.08).

Discussion

In this study we attempted to examine a wide range of demographic (sex, age and disease duration), disease related (motor and non-motor features) and genetic correlates for PS in PD. A total of 13 factors were examined in a multivariate analysis. A key strength of this study is the size of the population, 500 subjects, substantially larger than prior examinations of associated features for PS in PD. Our figure of 13% with PS in a PD population with a mean duration of 8.5 years is similar to the 15.8% seen in a population of 235 cases with a duration of 9.1 years previously reported in a population based study [14]. Results were confirmatory for several previously examined features, including some with inconsistent results in prior reports, and for others novel. In the literature, several demographic and disease related risk factors have been repeatedly reported in previous studies including age, cognitive dysfunction, depression and severity of PD. More advanced age or age of onset was found to be a risk in several studies [14, 28-30], but not others [31]. Similarly, duration of PD was associated with the presence of PS in some reports [29, 30, 32, 33], but not all [31]. We confirmed that age was strongly correlated with the occurrence of PS. We also found that duration of disease was a risk factor although this was less profound than age. The size of

our subject population included more than twice the number of cases previously examined for these risk factors (maximum number was 235) and demonstrates that both are important [14]. These findings confirm what most clinicians believe, that patients with advanced age, in particular, should be monitored closely for PS when prescribing anti-PD medications.

Our examination of other non-motor features also confirmed previous findings. An association between PS and cognitive dysfunction has been demonstrated in several recent cross-sectional and longitudinal studies [9, 14, 29, 30, 32, 33,34]. This is true in early PD as well, with an inverse correlation between MMSE score and the occurrence of psychosis[35]. Consistent with this literature, we found a statistically significant inverse trend between MMSE and risk of PS. It is possible that the MMSE is an insensitive measure of cognitive dysfunction in PD and perhaps the use of the Montreal Cognitive Assessment would detect a more robust association [36]. The non-motor feature most strongly associated with PS in our PD population was depression, measured with the BDI2, a validated measure in PD [37]. Although depression was considered to be a strong predictor for the development of hallucinations in some prior studies [2914, 30, 33], others have suggested otherwise [32, 38]. The relationship that cognitive dysfunction and depression have with PS in PD, may have important therapeutic implications. In patients with dementia and/or depression the use of acetylcholinesterase inhibitors and antidepressants have been shown to improve PS and may represent reasonable first lines of treatment before initiating antipsychotics in appropriate cases [39, 40].

In this study we asked a yes/no question regarding whether patients experienced either hypersomnia or insomnia and a significant association with PS was found. In most studies the relationship between PS and sleep surrounded the presence of abnormal dream phenomena such as REM Sleep Behavior Disorder Sleep disorder and vivid dreaming [2] but we did not address this. Sleep disorders such as fragmented sleep and excessive daytime sleepiness have long been thought to be closely correlated with hallucinations[30, 32, 41] and we found that patients with PS self report sleep problems such hypersomnia and insomnia more than non-PS patients. However, a recent longitudinal study of 89 cases suggested that they were not necessarily predictive [2].

Several studies have suggested that there is a correlation between overall motor disability and psychosis in PD using the UPDRS motor score [14, 28, 33] and Hoehn & Yahr stage [28, 29, 42]. One study examined specific clinical features of PD [28] as possible risks through examination of 166 PD patients with UPDRS motor examination. They found that lower tremor scores and higher rigidity, bradykinesia and postural instability scores were associated with PS. We did not confirm either finding. There was no association with the tremor subscore or GBS. We also used falling as a correlate but there also was no association. We did find a significant relationship between PS and FOG, not previously reported in studies where PS was the primary outcome. One study using exploratory and confirmatory factor analyses of motor features in 344 PD subjects (divided into two independent samples) found that PD divided by clustering of motor features into four independent factors; axial factor 2 relating specifically to FOG, speech and swallowing [43]. This particular factor correlated moderately to psychotic symptoms. This is the only

previous recognition of a relationship between FOG and PS. Whether this suggested share pathophysiology remains to be determined, but it does appear that patients with FOG need to be monitored more closely for PS.

There have been several attempts to evaluate genetic risk factors for hallucinations in PD. Genes examined included dopamine transporter gene polymorphisms [44], cholecystokinin (CCK) promoter polymorphisms [4546], *ACE* II genotype [47], $5HT_{2A}$ receptor or transporter genes [48] *APOE ε4* or *APOE ε2* [49], and COMT [49] all of which have had inconsistent or negative results. We selected genetic polymorphisms based on prior results indicating that they impact on risk of developing PD reasoning that a gene that affects the risk of disease might also affect disease progression and outcome; *MAPT*, *SNCA*-REP1, and *APOE* [19]. This analysis was largely exploratory. The *SNCA*-REP 261 allele, which is associated with a greater risk of developing PD [22], showed an increased risk which was borderline significant (p=.08). No other associations were seen.

There are several strengths of this study beyond the large sample size. They include the consecutive nature of data collection; diagnosis of PD and outcomes by movement disorder specialists; use of standardized measures such as UPDRS, BDI2, MMSE and the availability of genetic data.

Methodological limitations include the cross-sectional design, i.e., we do not know if some correlates (e.g., presence of FOG) preceded the occurrence of PS. We were not able to take into account any treatment related variables (levodopa equivalents, duration of therapy, use of adjunctive agents) for this analysis. These variables were not available for all of the subjects. However, the subjects were generally treated with comparable drug regimens (all were treated with levodopa and some with dopamine agonists, COMTI's, and fewer with MAOI's). It was our intent to focus on disease related issues as previous investigators [9, 14] did not find any associations with treatment related variables. While this represents a limitation of this study, it does not affect our major conclusions, i.e., that other disease-associated factors (demographic, motor and non-motor) also influence the development of psychosis. On the other hand, including treatment related variables could potentially help identify other disease-associated genes that were missed through gene-drug interactions. However, because of the frequent medication changes in PD patients longitudinal studies would be better for examining drug effects on PS. Confirmation of our findings in a large longitudinal, hypothesis driven study with more detailed measures of the clinical features and examination of other potential genetic predictors in GWAS would be important next steps.

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Table

Shown on this table are the numbers of patients with and without psychotic symptoms (PS) (row depicted “Number”) and the number (%) for variables for those with psychotic symptoms (column named “PS”) and without psychotic symptoms (column named “no PS”).

Predictors	**PS # (%)**	**No PS # (%)**	**Odds ratio**	**95% CI**	**P-value**	**P-value test for linear trend for continuous variables***
Number	63 (13)	437 (87)				
Sex						
Male	36 (57%)	273 (62%)	.96	.49-1.89	.91	
PD Duration						
<=4.6 yrs	5 (8)	150 (34)	1.00	Reference		
4.7-9.7	21 (33)	155 (36)	3.81	1.23-11.76	.02	
>9.7	37 (59)	132 (30)	5.33	1.68-16.89	.005	.03
Age						
< 63.7 yrs	6 (10)	163 (37)	1.00	Reference		
63.7-72.9	24 (38)	132 (30)	4.82	1.62-14.30	.005	
>72.9	33 (52)	142 (33)	6.25	2.09-18.74	.001	.01
Motor predictors						
GBS <=2.5	11 (18)	135 (31)	1.00	Reference		
GBS 3-5	14 (22)	186 (43)	0.48	0.18-1.28	.15	
GBS>5*	38 (60)	116 (27)	0.68	0.26-1.82	.45	0.59
Tremor subscore=0	25 (40)	140 (32)	1.00	Reference		
Tremor subscore=0.5-2.5	23 (37)	151 (35)	1.90	0.84-4.32	.13	
Tremor subscore>2.5	15 (24)	146 (33)	0.83	0.35-2.01	.68	.27
Freezing of gait	28 (44%)	54 (12%)	3.83	1.67-8.75	.002	
Falling	12 (19%)	20 (5%)	1.15	0.37-3.56	.81	
Non-motor predictors						
BDI2<=5	9 (14)	156 (36)	1.00	Reference		
BDI2 5.5-10	12 (19)	150 (34)	1.31	0.47-3.61	.61	
BDI2>10	42 (67)	131 (30)	5.02	2.04-12.33	.0004	<.0001
Sleep	40 (64%)	175 (40%)	2.00	1.03-3.89	0.04	

Predictors	PS # (%)	No PS # (%)	Odds ratio	95% CI	P-value	P-value test for linear trend for continuous variables*
MMSE =30	38 (60)	109 (25)	1.00	Reference		
MMSE=29-28	16 (25)	193 (44)	0.69	0.26-1.84	0.46	
MMSE<28	9 (14)	135 (31)	2.51	1.00-6.29	0.05	.03
Genetic predictors						
APOE ε4	17 (27%)	94 (22%)	1.16	0.53-2.52	.71	
APOE ε2	11 (17%)	78 (18%)	1.20	0.53-2.71	.67	
REP 257	25 (40%)	184 (42%)	1.09	0.53-2.27	.81	
REP 261	12 (19%)	54 (12%)	2.35	0.91-6.05	.08	
MAPT H1H1	45 (71%)	292 (67%)	1.57	0.75-3.26	.23	

*test for trend for continuous variables based on the p-value for the coefficient for the variable in the logistic model

**The univariate frequencies for GBS and PS status indicate that higher GBS is strongly related to higher risk of PS, while the multivariate-adjusted odds ratios indicate the opposite. This seeming contraction arises because GBS is positively correlated with other important variables in the model (age, duration, BDI, falling, and freezing) and negatively correlated with MMSE, all with highly significant ($p<0.0001$) correlations ranging from 0.2 to 0.4. After adjusting for all variables simultaneously in the multivariate logistic regression model, the apparent positive association between GBS and PS – judged by the unadjusted frequencies - completely goes away.