BRIEF REPORT

Psychotic-Spectrum Disorders With Comorbid Anxiety Are Predisposing Factors for Parkinson's Disease in a Case–Control Study

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Abstract

BACKGROUND: Multiple studies have demonstrated associations between psychiatric conditions and Parkinson's disease (PD) development; fewer have examined psychotic-spectrum disorders and PD development.

OBJECTIVE: The objective was to assess the prevalence of psychotic-spectrum disorders with and without depression and anxiety preceding a PD diagnosis.

METHODS: In this retrospective, case–control study of adults > 60 years of age, cases were identified by PD diagnosis and controls were identified in a 3:1 ratio by ambulatory encounter from 2015 to 2020. Psychiatric conditions were identified by diagnosis code up to 5 years prior to the index date. Conditional logistic regression was conducted to assess associations.

RESULTS: Among 13,998 patients, the odds of PD were 76% (95% confidence interval = 1.39–2.22) higher among those with psychotic-spectrum diagnoses. An additional anxiety diagnosis was associated with 166% (95% confidence interval = 1.35–5.25) higher odds of PD.

CONCLUSIONS: Awareness of psychiatric conditions, including psychotic-spectrum disorders with comorbid anxiety, can stratify individuals at higher risk of developing PD.

Introduction

Several mental health conditions have been examined as risk factors for the development of Parkinson's disease (PD), including anxiety, depression, and bipolar disorder.[1–6] Anxiety itself has been suggested as one of the earliest manifestations of PD.[1,4,5] Other psychiatric disorders are common among individuals who progress to PD.[7] Depression

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Anna Shvartsur, MD, Roy Eyal, MD, Nirmala D Ramalingam, MPP, Suketu Khandhar, MD, Michel Medina, MD, and Matthew E Hirschtritt, MD, MPH, designed the study. Kelli Peterman, MPH, acquired the data and conducted the data analyses. All authors contributed to the interpretation of data. Anna Shvartsur, MD, drafted the initial version of the paper. All authors revised the manuscript for important intellectual content and approved the final draft for submission.

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is often comorbid in PD.[8] In the general population, psychiatric comorbidity is also prevalent.[9–11]

A few studies have examined psychotic-spectrum disorders, like schizophrenia, as risk factors for developing PD.[12–14] Overlapping genetic variants have been identified between schizophrenia and PD.[15] However, determining whether there is a causal association between certain mental health conditions and PD—and in what direction—is currently unclear. For instance, antipsychotic medications may cause extrapyramidal side effects that mimic the motor features of PD.[16,17] Parkinsonism refers to symptoms of rigidity, bradykinesia, or tremors that are often seen in PD or may be secondary to medications, toxins, or other conditions.[16,17] Patients with psychotic-spectrum disorders who are antipsychotic-naïve may be more likely than nonaffected individuals to experience parkinsonism and dyskinesia as part of the progression of their psychiatric illness.[18]

Recent studies have attempted to disentangle the complex associations among psychotic-spectrum disorders and PD. Cross-sectional studies from Scotland and Spain that assessed for physical health comorbidities among patients with and without schizophrenia demonstrated an increased prevalence of PD among patients with schizophrenia.[19,20] A prospective study from Taiwan that followed a general community cohort for up to 6 years showed a 2.38-fold increased risk of later development of PD among patients with a mental health diagnosis, with schizophrenia specifically associated with the highest risk.[12] A retrospective study from Hungary found a 2-fold higher prevalence of schizophrenia within a 13-year period preceding PD when compared to patients with ischemic cerebrovascular lesions.[13] None of the studies mentioned above assessed for secondary causes of parkinsonism, such as extrapyramidal side effects of antipsychotics or atypical parkinsonism. However, a retrospective study from Finland that found a higher prevalence of psychotic-spectrum disorders preceding PD compared to the general population did exclude cases of secondary parkinsonism.[14]

Having studies that accurately differentiate PD from secondary causes of parkinsonism is important for diagnostic clarity and treatment planning. The present study aimed to accurately aggregate a cohort of patients with PD within a diverse, Northern California–based population and to characterize psychotic-spectrum disorders preceding PD. The authors aimed to then examine whether psychotic-spectrum disorders with concomitant anxiety or depression further exacerbated the risk for PD. Understanding the psychiatric risk factors for PD can help clinicians, especially those in the mental health field, improve risk stratification for older individuals with specific psychiatric comorbidities who may be at higher risk of developing PD in the future.

Methods

STUDY POPULATION

This paper describes a retrospective, case–control study of Kaiser Permanente Northern California members aged ≥ 60 years. Kaiser Permanente Northern California is a large integrated health care system that uses an electronic health record system. Cases were identified by date of initial diagnosis of PD between January 1, 2015, and December 31, 2020 (index date). Controls were identified in a 3:1 ratio by ambulatory encounter in the same facility, using any clinic or service within the matched facility, within 30 days before or after the matched PD case index date. PD diagnosis on the problem list at the matched index date and history of head injury within 5 years of the case index date were exclusion criteria for controls. Cases were matched by sex, age, encounter date, and facility location. Cases and controls had to have ≥ 5 years of continuous Kaiser Permanente Northern California insurance preceding the index date. Insurance was considered continuous if the gap between stopping and starting coverage was ≤ 31 days. Cases with a diagnosis of parkinsonism, a history of head injury < 5 years prior to the index date, age of < 60 years at index, no identifiable facility location, and no matching control were excluded from this study. This study was approved by Kaiser Permanente Northern California's Institutional Review Board. The Institutional Review Board waived the requirement to obtain informed consent as allowed under §46.116(d).

STUDY VARIABLES

Parkinson's Disease

PD diagnosis was extracted from the Kaiser Permanente Northern California problem list, which contains patients' ongoing diagnoses and conditions. This method was determined upon consultation with Kaiser Permanente Northern California neurologists, who confirmed that per Kaiser Permanente Northern California practices, PD diagnosis is placed onto the problem list by a

neurologist after formal initial evaluation for PD. The first date of a PD diagnosis on the problem list was used as the index date.

Mental Health Conditions

Depressive disorders, anxiety disorders, and psychotic-spectrum disorders were studied as exposures. These were identified by International Classification of Diseases, 9th and 10th Revisions, diagnosis codes up to 5 years prior to the index date (Supplemental Table 1). The psychotic-spectrum disorders included were schizophrenia, schizoaffective disorder, delusional disorder, brief psychotic disorder, schizophreniform disorder, schizotypal disorder, unspecified psychosis not due to substances or known physiologic conditions, and other selected unspecified psychosis. Mental health diagnoses from any encounter (including inpatient, ambulatory, and emergency room settings), as well as the Kaiser Permanente Northern California problem list, were included.

Covariates

Race, ethnicity, tobacco, alcohol, and other substance use were determined based on self-reported electronic health record data at the index date. To determine socioeconomic status (SES), patients' addresses were matched to American Community Survey (ACS) census block data. Index dates from 2010 to 2018 were matched with the corresponding ACS year, whereas dates from 2019 to 2020 were matched with the 2019 ACS data. Low SES was determined if ≥ 20% of the household incomes in that census block were below the federal poverty level or if > 25% of the residents in that census block held less than a high school degree.

STATISTICAL ANALYSES

Bivariate analyses were performed using unadjusted conditional logistic regression to assess associations between mental health disorders, other patient characteristics, and PD. Separate multivariable analyses were performed using conditional logistic regression to assess the relationship between each mental health condition and PD. Multivariable analyses controlled for race and ethnicity, SES, and alcohol, tobacco, and other substance use. Unadjusted conditional logistic regression models that reached significance ($P < .05$) were further adjusted for race and ethnicity, SES, and alcohol, tobacco, and other substance use. Statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC).

Results

Among 13,998 total patients (3501 PD patients), 61.7% were male, and 74.1% were ages ≥ 70 years (32.2% were > 80). Race and ethnicity included the following: 69.9% White, 12.7% Asian/Pacific Islander, 11.5% Hispanic, 5.5% Black, 0.4% other/unknown, and 0.6% missing data. A significantly lower percentage of Black patients had a PD diagnosis compared to White patients ($P < .001$). Patients with PD had significantly lower alcohol ($P < .0002$) and tobacco use ($P < .0001$). See Table 1 for the aforementioned results. Race and ethnicity were not significantly associated with mental health diagnoses in the PD cohort (Supplemental Tables 2 and 3).

The following mental health conditions were associated with higher odds of PD (Table 2): anxiety disorder: odds ratio (OR) = 1.44 [95% confidence interval (CI) = 1.31–1.58]; depressive disorder: OR = 1.40 (95% CI = 1.27–1.54); and psychotic-spectrum disorder: OR = 1.76 (95% CI = 1.39–2.22). Among those diagnosed with a psychotic-spectrum disorder (n = 327), an additional diagnosis of anxiety was associated with 2.66 (95% CI = 1.35–5.25) times higher odds of PD (Table 2). Among patients diagnosed with a psychotic-spectrum disorder, depressive disorders were not significantly associated with higher odds of PD in the unadjusted conditional regression model; a further adjusted conditional regression model was not executed due to the low likelihood of significance (Table 2 and Supplemental Table 4).

Discussion

The authors examined the associations among psychotic, depressive, and anxiety disorders preceding the development of PD among a large, diverse sample of Northern California adults and found higher odds of PD among patients with preceding psychotic-spectrum disorders compared to age- and sex-matched controls. In addition, the authors found that among this subset, patients with comorbid anxiety disorders had higher odds of PD, whereas those with comorbid depressive disorders did not. It is important to note that anxiety itself has been considered a potential early nonmotor manifestation of PD rather than a comorbidity or risk factor for PD, and thus the existence of anxiety later in life may be an early sign

Variables N (%)	Total (%) (N = 13,998)	Control (%) (N = 10,497)	PD (%) (N = 3501)	*P* Value[a,b]
Sex				—
Female	5358 (38.3)	4017 (38.3)	1341 (38.3)	
Male	8640 (61.7)	6480 (61.7)	2160 (61.7)	
Age, y				—
60–69	3589 (25.6)	2685 (25.6)	904 (25.8)	
70–79	5952 (42.5)	4484 (42.7)	1468 (41.9)	
≥ 80	4457 (31.8)	3328 (31.7)	1129 (32.2)	
Race and ethnicity				
Missing	89 (0.6)	66 (0.6)	23 (0.7)	
Asian/Pacific Islander	1768 (12.7)	1311 (12.6)	457 (13.1)	.811
Black	763 (5.5)	621 (6.0)	142 (4.1)	< .001
Hispanic	1596 (11.5)	1202 (11.5)	394 (11.3)	.529
Other/unknown	59 (0.4)	38 (0.4)	21 (0.6)	.081
White	9723 (69.9)	7259 (69.6)	2464 (70.8)	Ref
Low SES				
Missing	3 (0.0)	2 (0.0)	1 (0.0)	
No	12,093 (86.4)	9036 (86.1)	3057 (87.3)	Ref
Yes	1902 (13.6)	1459 (13.9)	443 (12.7)	.050
Anxiety disorder				
No	10,960 (78.3)	8372 (79.8)	2588 (73.9)	Ref
Yes	3038 (21.7)	2125 (20.2)	913 (26.1)	< .0001
Depressive disorder				
No	11,174 (79.8)	8506 (81.0)	2668 (76.2)	Ref
Yes	2824 (20.2)	1991 (19.0)	833 (23.8)	< .0001
Psychotic-spectrum disorder				
No	13,671 (97.7)	10,286 (98.0)	3385 (96.7)	Ref
Yes	327 (2.3)	211 (2.0)	116 (3.3)	< .0001
Alcohol use				
No	13,324 (95.2)	9950 (94.8)	3374 (96.4)	Ref
Yes	674 (4.8)	547 (5.2)	127 (3.6)	.0002
Tobacco use				
No	12,609 (90.1)	9364 (89.2)	3245 (92.7)	Ref
Yes	1389 (9.9)	1133 (10.8)	256 (7.3)	< .0001
Other substance use				
No	13,665 (97.6)	10,236 (97.5)	3429 (97.9)	Ref
Yes	333 (2.4)	261 (2.5)	72 (2.1)	.146

Table 1: Patient Demographics and Characteristics

[a] Values from unadjusted conditional logistic regression.

[b] Statistical tests not performed on variables used for matching (age, sex).

PD = Parkinson's disease; Ref = reference; SES = socioeconomic status.

of PD in some cases rather than a risk factor for its development.[1,4,5]

A significantly lower percentage of Black patients was found to have PD compared to White patients, aligning with the increased risk of PD seen in White individuals. Alcohol, tobacco, and other substance use were relatively low in cases and controls; alcohol and tobacco use were significantly lower in PD cases, which may be related to

Disorder	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Association between anxiety, depression, psychotic-spectrum disorders and PD (N = 13,998)		
Anxiety	1.41 (1.29–1.55)	1.44 (1.31–1.58)
Depression	1.34 (1.22–1.47)	1.40 (1.27–1.54)
Psychotic-spectrum	1.67 (1.33–2.10)	1.76 (1.39–2.22)
Association between anxiety and depression disorders and PD, in cohort with preceding psychotic-spectrum disorder (N = 327)		
Anxiety	2.29 (1.19–4.41)	2.66 (1.35–5.25)
Depression	1.15 (0.62–2.13)	—

Table 2: Conditional Logistic Regression: Associations Between Mental Health Disorders and Parkinson's Disease

[a] Models adjusted for race and ethnicity, low SES, alcohol use, tobacco use, and substance use.

CI = confidence interval; OR = odds ratio; PD = Parkinson's disease; SES = socioeconomic status.

behavior changes prompted by declining health associated with PD diagnosis vs other factors.

Differentiating PD from secondary causes of parkinsonism has been a limitation in previous studies examining psychiatric risk factors for PD.[12,13,19,20] This is an important consideration because certain mental health conditions—notably psychotic-spectrum disorders—and their treatments may lead to symptoms of parkinsonism and be misclassified as PD. Patients with psychotic disorders who are naïve to antipsychotic medications may exhibit parkinsonism as their illness progresses, and patients who take antipsychotic medications may experience side effects mimicking parkinsonism.[16–18] Diagnostic clarity is therefore vital for differentiating causal relationships between mental health conditions and subsequent development of PD. The present study aimed to address this concern by including cases of PD that were placed on patients' problem lists, as these are placed by a neurologist after initial evaluation for PD and by actively excluding parkinsonism.

One retrospective study from Finland that excluded cases with secondary causes of parkinsonism reported an increased prevalence of psychotic-spectrum disorders prior to PD development, which aligns with results from the present study.[14] In addition to excluding secondary causes of parkinsonism, the present study examined whether comorbid anxiety or depressive disorders further increased the risk of later development of PD. The authors found that anxiety disorders increased this risk significantly but that an additional depressive disorder diagnosis did not. This finding may encourage clinicians to increase vigilance in monitoring for PD in patients with psychotic-spectrum disorders and comorbid anxiety disorders.

Strengths of the present study include a diverse patient sample in a large integrated health care delivery system. Efforts were made to optimize diagnostic clarity of PD and exclude secondary causes of parkinsonism, as mentioned above. A thorough chart review of a randomly selected subset of the present study cohort was conducted to validate the methods used. Chart review of several parkinsonism cases showed that most tended to be secondary causes of parkinsonism (ie, drug-induced), thus all parkinsonism diagnoses were excluded in the PD cohort. Controlling for whether patients with psychotic-spectrum disorders were taking antipsychotic medications, the class of medication (typical vs atypical), the doses prescribed, the timeline of when they were taken, and whether extrapyramidal side effects developed would provide great value, as the lack of this information is an important limitation because the inability to control for such medication use could overstate the association between psychotic-spectrum disorders and PD.

There is still concern for missed or inaccurate diagnoses (eg, due to variations across practitioners). Additionally, obtaining accurate onset dates of PD is challenging given the possibility that patients may experience undetected symptoms or may not present for evaluation of symptoms prior to the date of diagnosis captured in the medical record. Similarly, the authors were unable to confirm the onset of mental health diagnoses. The accuracy of the mental health diagnoses, the potential for misdiagnosis, and the differences in screening practices are other limitations. Patients who eventually developed PD may have had prodromal PD symptoms that could mimic symptoms of depression, such as masked faces, apathy, and bradykinesia, leading to misdiagnosis with a mental health disorder. Alternatively, these patients may have developed depression or anxiety symptoms as a response to certain early symptoms of PD (eg, sleep disturbance, rigidity) prior to official PD diagnosis. Identifying the timeline and severity of psychotic-spectrum disorders, anxiety, and depressive disorders, as well as confirming the diagnoses, would be helpful aims for future studies.

There is increasing evidence for psychotic-spectrum disorders being a risk factor for the development of PD. Psychotic-spectrum disorders with comorbid anxiety disorders may further point to this risk, with the existence of anxiety potentially indicating the start of PD. These conditions are therefore important for clinicians to be aware of in order to improve risk stratification for PD, identify early nonmotor signs of PD more readily, develop preventive interventions, and better coordinate treatment.

Previously Presented
This work is based upon an earlier version that was presented as a poster at the 148th Annual Meeting of the American Neurological Association in Philadelphia, PA, USA. It is used with permission.

Data-Sharing Statement
Data are available upon request. Readers may contact the corresponding author to request underlying data.

Supplementary Materials
Supplemental material is available at: https://www.thepermanentejournal.org/doi/10.7812/TPP/24.131#supplementary-materials.

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