ARTICLE

Bipolar disorder and risk of Parkinson disease

A nationwide longitudinal study

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Abstract

Objective

To evaluate the risk of Parkinson disease (PD) among patients with bipolar disorder (BD).

Methods

Using the Taiwan National Health Insurance Research Database, we examined 56,340 patients with BD and 225,360 age- and sex-matched controls between 2001 and 2009 and followed them to the end of 2011. Individuals who developed PD during the follow-up period were identified.

Results

Patients with BD had a higher incidence of PD (0.7% vs 0.1%, $p < 0.001$) during the follow-up period than the controls. A Cox regression analysis with adjustments for demographic data and medical comorbid conditions revealed that patients with BD were more likely to develop PD (hazard ratio [HR] 6.78, 95% confidence interval [CI] 5.74–8.02) than the control group. Sensitivity analyses after exclusion of the first year (HR 5.82, 95% CI 4.89–6.93) or first 3 years (HR 4.42; 95% CI 3.63–5.37) of observation showed consistent findings. Moreover, a high frequency of psychiatric admission for manic/mixed and depressive episodes was associated with an increased risk of developing PD.

Conclusion

Patients with BD had a higher incidence of PD during the follow-up period than the control group. Manic/mixed and depressive episodes were associated with an elevated likelihood of developing PD. Further studies are necessary to investigate the underlying pathophysiology between BD and PD.

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Glossary

BD = bipolar disorder; **CI** = confidence interval; **HR** = hazard ratio; **ICD-9-CM** = *International Classification of Diseases, 9th revision, clinical modification*; **NHI** = National Health Insurance; **NHIRD** = National Health Insurance Research Database; **NTD** = New Taiwan Dollar; **PD** = Parkinson disease.

Parkinson disease (PD) is one of the most common neurodegenerative diseases, with a prevalence of 1% in the population >60 years of age.[1] It results predominantly from dopamine depletion in the substantia nigra pars compacta,[2] and it is clinically defined as a combination of bradykinesia with resting tremor or rigidity.[3]

While patients with major depressive disorder were found to have a higher risk of developing PD later in life, few studies have examined the potential role of bipolar disorder (BD), a psychiatric disorder characterized by recurrent episodes of mania/hypomania and depression, in the risk of subsequent PD. A hospital registry study revealed that people who experienced manic or depressive episodes had an elevated risk of being diagnosed with PD.[4] However, the temporal association between BD and subsequent PD was not determined in the case-control study with a large sample size and a longitudinal follow-up study design.[5] Small sample sizes and differences in the study methodology and data sources of the previous studies resulted in uncertainty about the actual risk of PD among patients with BD.

We investigated the risk of developing PD among patients with BD by using the Taiwan National Health Insurance (NHI) Research Database (NHIRD) with a large sample size and a longitudinal study design. We hypothesized that patients with BD would have an increased risk of PD compared with the control group.

Methods

Data source

The Taiwan NHI Program, established in 1995, is a universal single-payer system that provides compulsory health insurance to almost all residents of Taiwan (≈23 million people); its coverage rate was ≈99.6% at the end of 2010. The NHIRD was released and audited by the Department of Health and Bureau of the NHI Program. It provides comprehensive information about insured patients such as demographic data (birth date, sex, residential location, income status) and clinical visits (visit dates and medical diagnoses). To protect patient privacy, every patient is assigned a unique and anonymous identifier by the National Health Research Institutes before the data are released to researchers; thus, a patient can be followed up continuously with the unique identifier. A nationwide database with a large sample size can minimize selection bias. The ICD-9-CM was used to diagnose diseases during the study period. The NHIRD has been used extensively in epidemiologic studies in Taiwan.[6–8]

Standard protocol approvals, registrations, and patient consents

The Institutional Review Board of the Taipei Veterans General Hospital approved this study. Informed consent was waived because the NHIRD consists of deidentified secondary data.

Study population

Adults ≥20 years of age who were diagnosed as having BD (ICD-9-CM codes 296 except 296.2x, 296.3x, 296.9x, and 296.82) by board-certificated psychiatrists between January 1, 2001, and December 31, 2009, and who had no history of PD and related diseases (ICD-9-CM code 332) before enrollment were included in the BD cohort. The time of enrollment was defined as the time of BD diagnosis. Individuals of the age-, sex-, time of enrollment–, medical comorbidity–, income-, and level of urbanization–matched (1:4) control cohort were randomly selected after elimination of the study cases, individuals who had been diagnosed with BD at any time, and individuals with PD. A diagnosis of PD (ICD-9-CM code 332.0) made by board-certificated neurologists was recorded during the follow-up period (from enrollment to December 31, 2011, or until death). Medical comorbid conditions included cerebrovascular diseases, traumatic brain injury, hypertension, dyslipidemia, and diabetes mellitus. The frequency (times per year) of psychiatric admission for BD was assessed and regarded as an indicator of disease severity of BD in our study. Furthermore, the frequencies of psychiatric admission for manic/mixed and depressive episodes of BD were examined separately so that the association between manic/mixed and depressive episodes and the risk of PD could be clarified. Income was defined as low (monthly income below New Taiwan Dollar [NTD] 15,840), medium (monthly income NTD 15,840–25,000), or high (monthly income >NTD 25,000). Values of NTD 15,840 represented monthly salaries at tier 1 according to the 38-tier insured amount designed by the NHI. The average salary after graduation was NTD 25,000 according to the data released in 2015 by the Ministry of Labor in Taiwan. Level of urbanization (levels 1–5, with level 1 the most urbanized region and level 5 the least urbanized region) was also assessed.[9]

Statistical analysis

For between-group comparisons, the F test was used for continuous variables and the Pearson χ^2 test was used for nominal variables when appropriate. A Cox regression analysis with adjustments for demographic data (age, sex, income, level of urbanization) and medical comorbid conditions (cerebrovascular diseases, traumatic brain injury, hypertension, dyslipidemia, and diabetes mellitus) was performed to

investigate the risk of developing PD among patients with BD and the control group. Subanalyses stratified by age group (<65 vs ≥65 years) were conducted to further assess the relationship between BD and the risk of developing PD. Cox regression analyses were used to clarify the association between the frequency of psychiatric admission for BD (total, manic/mixed, and depressive episodes) and the risk of PD among patients with BD. To assess with robustness of our study, sensitivity analyses were performed to minimize the influence of potential bias. We investigated the association between BD and PD after excluding the first year or first 3 years of observation in model 1. To eliminate the confounding effect of antipsychotics-related parkinsonism, we conducted sensitivity analyses after excluding those with PD who were exposed to any antipsychotics before 3, 6, 12, and 36 months of PD diagnosis in model 2. A 2-tailed value of $p < 0.05$ was considered statistically significant. All data processing and statistical analyses were performed with SPSS version 17 (SPSS Inc., Chicago, IL) and Statistical Analysis Software version 9.1 (SAS Institute, Cary, NC).

Data availability

The NHIRD was released and audited by the Department of Health and Bureau of the NHI Program for the purpose of scientific research (nhird.nhri.org.tw/). NHIRD can be obtained through formal application that is regulated by Department of Health and Bureau of the NHI Program.

Results

A total of 56,340 patients with BD and 225,360 age- and sex-matched controls were enrolled in our study; their average age was 39.98 ± 13.63 years. The patients with BD had a higher incidence of developing PD (0.7 vs 0.1%, $p < 0.001$) and a shorter duration from enrollment to diagnosis of PD during the follow-up period than the control group (table 1). The prevalence of cerebrovascular diseases, traumatic brain injury, hypertension, dyslipidemia, and diabetes mellitus did not differ between the 2 groups (table 1).

Cox regression analyses with adjustments for demographic data and medical comorbid conditions showed that the adult (hazard ratio [HR] 12.02, 95% confidence interval [CI] 9.33–15.51) and geriatric (HR 3.87, 95% CI 3.05–4.09) patients with BD were more likely to develop PD during the follow-up period than the control group (table 2). Furthermore, patients with a high frequency of psychiatric admission for BD exhibited an increased risk of developing PD compared with those patients who were admitted less than once per year (table 3). The frequency of psychiatric admission for manic/mixed (1–2 per year: HR 4.02, 95% CI 2.44–6.61; >2 per year: HR 6.29, 95% CI 4.07–9.73) or depressive (1–2 per year: HR 2.67, 95% CI 1.26–5.66; >2 per year: HR 6.19, 95% CI 3.18–12.02) episodes was related to the increased likelihood of subsequent PD (table 3). Sensitivity analyses after exclusion of the first year (HR 5.82, 95% CI 4.89–6.93) or first 3 years (HR 4.42, 95% CI 3.63–5.37) of observation showed consistent findings: patients with BD were associated with an elevated risk of subsequently developing PD in later life (table 4). Sensitivity analyses after the exclusion of antipsychotics exposure before PD diagnosis also supported the consistent association between BD and subsequent PD (table 4). The Kaplan-Meier survival curve with the log-rank test indicated that patients with BD had a higher risk of developing PD ($p < 0.001$) than the control group (figure).

Discussion

Our results supported the study hypotheses that patients with BD would have an increased risk of developing PD compared with the controls without BD. The significant trend of an increased risk of PD was shown in both adult patients and those >65 years of age. In addition, manic/mixed and depressive episodes may be related to an increased risk of developing PD later in life. Furthermore, patients who had a high frequency of psychiatric admission for BD exhibited an increased risk of subsequently developing PD.

Consistent with a 6-year follow-up study of 1,203 patients with BD,[10] our study suggested a higher PD risk among patients with BD than the controls by using the population-based dataset with a longer follow-up period and full adjustment for medical comorbid conditions and demographic data. Previous studies found that the number of mood episodes was associated with the greater progressive deterioration in cognitive function[11] and brain morphology in BD.[12,13] An increase in dopaminergic transmission in mania and the converse in depression may play important roles in the progressive deterioration of BD.[14,15] However, whether the number of mood episodes and different mood states of BD are related to the higher risk of developing PD later in life remains unclear. In the current study, defining the mood episodes as the frequency of psychiatric admission, we found that the higher frequency of psychiatric admission was related to the greater risk of developing PD. We further examined the risk of subsequent PD stratified by psychiatric admissions due to different mood states and determined that both manic/mixed and depressive episodes are associated with an elevated risk of developing PD. The association between depression and PD has been well documented. Depressive symptoms often precede the onset of motor symptoms in patients with PD,[5] and a diagnosis of depression was associated with an increased risk of PD,[16] indicating that depression in patients with PD is not simply a symptom of the disease itself. The association between mania/hypomania and PD has rarely been reported. The reason may be that when psychiatric symptoms occur during dopaminergic treatment for PD, they may be considered a drug-induced effect; however, when BD exists before PD, PD may be labeled as iatrogenic parkinsonism.

Because PD incidence and prevalence increased with age and lower income and were slightly higher in men than in women,[17]

Table 1 Demographic characteristics and incidence of PD among patients with BD and controls

	Patients with BD (n = 56,340)	Controls (n = 225,360)	*p* Value
Age at enrollment (SD), y	39.98 (13.63)	39.98 (13.64)	0.932
Sex, n (%)			1.000
Male	23,871 (42.4)	95,484 (42.4)	
Female	32,496 (57.6)	129,876 (57.6)	
Frequency of psychiatric admission for bipolar disorder, n (%)			
<1/y	53,127 (94.3)		
1–2/y	1,820 (3.2)		
>2/y	1,393 (2.5)		
Frequency of psychiatric admission for manic/mixed episode, n (%)			
<1/y	54,581 (96.9)		
1–2/y	961 (1.7)		
>2/y	798 (1.4)		
Frequency of psychiatric admission for depressive episode, n (%)			
<1/y	55,575 (98.9)		
1–2/y	541 (1.0)		
>2/y	224 (0.4)		
Incidence of PD, n (%)	372 (0.7)	222 (0.1)	<0.001
Excluding antipsychotics exposure before 3 mo of diagnosis	159 (0.3)	201 (0.1)	<0.001
Excluding antipsychotics exposure before 6 mo of diagnosis	136 (0.2)	196 (0.1)	<0.001
Excluding antipsychotics exposure before 1 y of diagnosis	115 (0.2)	193 (0.1)	<0.001
Excluding antipsychotics exposure before 3 y of diagnosis	64 (0.1)	181 (0.1)	0.018
Age at diagnosis of PD (SD), y	64.25 (11.63)	72.99 (11.72)	<0.001
Duration between enrollment and PD (SD), y	4.23 (3.02)	6.50 (2.78)	<0.001
Medical comorbid conditions, n (%)			
Cerebrovascular diseases	2,962 (5.3)	11,848 (5.3)	0.999
Traumatic brain injury	4,105 (7.3)	16,420 (7.3)	0.999
Hypertension	12,066 (21.4)	48,264 (21.4)	1.000
Dyslipidemia	9,855 (17.5)	39,420 (17.5)	1.000
Diabetes mellitus	6,769 (12.0)	27,076 (12.0)	1.000
Level of urbanization, n (%)			1.000
1 (Most urbanized)	19,502 (29.3)	66,008 (29.3)	
2	19,912 (35.3)	79,648 (35.3)	
3	7,609 (13.5)	30,436 (13.5)	
4	7,524 (13.4)	30,096 (13.4)	
5 (Most rural)	4,793 (8.5)	19,172 (8.5)	
Income-related insured amount, n (%)			<0.001
≤15,840 NTD/mo	24,648 (43.7)	75,454 (33.5)	

Continued

Table 1 Demographic characteristics and incidence of PD among patients with BD and controls *(continued)*

	Patients with BD (n = 56,340)	Controls (n = 225,360)	*p* Value
15,841–25,000 NTD/mo	19,780 (35.1)	85,694 (38.0)	
≥25,001 NTD/mo	11,912 (21.1)	64,212 (28.5)	

Abbreviations: BD = bipolar disorder; NTD = New Taiwan Dollar; PD = Parkinson disease.

we matched age, sex, income, and urbanization between patients with BD and controls. To improve the diagnostic validity of PD in our study, we used only the ICD-9-CM code 332.0 (primary PD) and excluded code 332.1 (secondary parkinsonism) to define the PD diagnosis. Lee et al.[18] reported that the accuracy of PD diagnosis was ≈95% in the Taiwan NHIRD. Furthermore, we performed the sensitivity analyses using the strictest method to define primary PD diagnosis after excluding antipsychotics exposure before 3, 6, 12, and 36 months of diagnosis and found consistent findings of the significant temporal association between BD and PD.

Numerous mechanisms may be involved in BD and PD neurodegeneration, including epigenetic alterations, inflammatory processes, and neurotransmission dysfunction. Several lines of evidence suggest that the 2 diseases may share common underlying mechanisms and demonstrated that impaired dopaminergic neurotransmission may contribute to the pathogenesis of BD and PD.[14,19] In addition, serotonin plays a pivotal role in the pathophysiology of BD,[20] and patients with PD had reduced serotonergic activity.[21] However, it should be noted that a single monoamine may not be responsible for the heterogeneous phenotypes of neuropsychiatric disorders. In addition, serum tumor necrosis factor-α and interleukin-6 levels were shown to be higher in those with manic, depressive, and mixed episodes than in controls.[22] Chronic inflammation has been reported to contribute to the progressive loss of nigral dopaminergic neurons in patients with PD.[23,24] The influence of neuroinflammatory responses in the association of BD and PD warrants further investigation.

The strengths of our study are the large, well-defined sample of patients and the longitudinal study design. Our study provides evidence for the association between BD and PD and emphasizes the need to investigate the problems raised by physiopathologic interpretations and therapeutic approaches. Moreover, our data reveal that patients with BD <65 years of age had an increased risk of PD. Although there is a lack of consensus on the cutoff age for early-onset PD, numerous studies have indicated the role of genetics in patients with early-onset PD.[25] A genome-wide association study concluded that BD may have little genetic overlap with PD.[26] Future genetic research should examine whether a link exists between BD and PD risk alleles, and additional experiments are required to obtain a deeper understanding of the mechanisms involved in the pathogenesis of PD and BD. In addition, medical practitioners should be aware that the risk of subsequent PD should be particularly considered in patients with BD, especially those with multiple psychiatric admissions for mood episodes.

Some study limitations should be addressed. First, only those who sought medical help for the diagnosis and treatment of

Table 2 Risk of developing PD among patients with BD and controls[a]

	HR (95% CI)		
	Age <65 y	Age ≥65 y	Total
BD			
Presence	12.02 (9.33–15.51)	3.87 (3.05–4.09)	6.78 (5.74–8.02)
Absence	1 (Referent)	1 (Referent)	1 (Referent)

Abbreviations: BD = bipolar disorder; CI = confidence interval; HR = hazard ratio; PD = Parkinson disease.
[a]Adjusted by demographic data (age, sex, income, level of urbanization) and medical comorbid conditions (cerebrovascular diseases, traumatic brain injury, hypertension, dyslipidemia, and diabetes mellitus).

Table 3 Risk of developing PD among patients with BD based on frequency of psychiatric admission for BD[a]

	HR (95% CI)
Frequency of psychiatric admission for BD	
<1/y	1 (Referent)
1–2/y	3.13 (2.07–4.74)
>2/y	5.62 (3.97–7.96)
Frequency of psychiatric admission for manic/mixed episode	
<1/y	1 (Referent)
1–2/y	4.02 (2.44–6.61)
>2/y	6.29 (4.07–9.73)
Frequency of psychiatric admission for depressive episode	
<1/y	1 (Referent)
1–2/y	2.67 (1.26–5.66)
>2/y	6.19 (3.18–12.02)

Abbreviations: BD = bipolar disorder; CI = confidence interval; HR = hazard ratio; PD = Parkinson disease.
[a] Adjusted by demographic data (age, sex, income, level of urbanization) and medical comorbid conditions (cerebrovascular diseases, traumatic brain injury, hypertension, dyslipidemia, and diabetes mellitus).

Table 4 Sensitivity analyses of developing PD among patients with BD and controls

	Model 1,[a] HR (95% CI)			Model 2,[a] HR (95% CI)			
	Total	>1 y[b]	>3 y[b]	Excluding antipsychotics exposure before 3 mo of diagnosis	Excluding antipsychotics exposure before 6 mo of diagnosis	Excluding antipsychotics exposure before 1 y of diagnosis	Excluding antipsychotics exposure before 3 y of diagnosis
BD							
Presence	6.78 (5.74–8.02)	5.82 (4.89–6.93)	4.42 (3.63–5.37)	3.21 (2.63–4.00)	2.85 (2.28–3.54)	2.45 (1.94–3.09)	1.46 (1.10–1.94)
Absence	1 (Referent)	1 (Referent)	1 (Referent)	1 (Referent)	1 (Referent)	1 (Referent)	1 (Referent)

Abbreviations: BD = bipolar disorder; CI = confidence interval; HR = hazard ratio; PD = Parkinson disease.
[a] Adjusted by demographic data (age, sex, income, level of urbanization) and medical comorbid conditions (cerebrovascular diseases, traumatic brain injury, hypertension, dyslipidemia, and diabetes mellitus).
[b] Excluding the first or first 3-year observation period.

Figure Survival curve of developing Parkinson disease among patients with bipolar disorder and controls

neuropsychiatric illnesses were identified. Therefore, the identification of patients may be biased and may have resulted in weakening of the observed link. However, the patients with BD or PD identified in our study were diagnosed by board-certified psychiatrists or neurologists, yielding an improved diagnostic validity. Furthermore, we used a series of sensitivity analyses to reconfirm the temporal association between BD and the risk of PD. Second, the NHIRD did not provide information on family history and environmental factors. The prevalent perspective on the etiologic factors in PD has changed from a sporadic basis to one in which genetic predisposition is considered a major contributor to the underlying cause.[27] A direct link between environmental mitochondrial toxins and PD has been suggested.[28] An examination of the influence of these factors may further elucidate the role of genetic predisposition and environmental factors in the development of neurobiological vulnerability to PD. Third, neuroleptic drugs used to treat patients with BD might increase the risk of iatrogenic parkinsonism. Although we performed sensitivity analyses after excluding antipsychotics exposure, the inclusion of false-positives may be still a concern. Fourth, mood episodes of BD may be clinically underestimated by the definition of the frequency of psychiatric admission. However, the psychiatric admission was a robust marker of disease (mania or depression) severity. The definite association between different mood episodes of BD and neuroprogression requires further investigation.

Our population-based longitudinal study found that patients with BD had an increased risk of developing PD later in life compared to the controls without BD after adjustment for demographic data and medical comorbid conditions. Manic/mixed and depressive episodes were associated with an increased risk of PD. Further studies are required to investigate

the underlying pathophysiology between BD and subsequent PD.

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Disclosure

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