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Increased risk of gout among patients with bipolar disorder: A nationwide population-based study

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ABSTRACT

This study aims to explore the association between bipolar disorder and the risk of gout using a nationwide population-based dataset. We used the 1996–2006 data from the Taiwan National Health Insurance Research Database. The study cohort comprised 24,262 patients who had visited outpatient departments for the treatment of bipolar disorder in the year 2000. A total of 121,310 enrollees matched with the study group in terms of age and gender, and were selected as the comparison cohort. Each patient was tracked 6 years from the index outpatient visit in 2000 until 2006 to identify all who had developed gout. Cox proportional hazard regressions were performed to compute the 6-year gout-free survival rate, adjusting for other variables. We found that gout occurred among 16.4% of the patients with bipolar disorder and 13.6% of the patients in the comparison cohort between 2000 and 2006 ($P<0.001$). After adjusting for potential confounders, the regression analysis shows that the hazard of developing gout during the 6-year follow-up period was 1.19 greater (95% confidence interval (CI) = 1.10–1.24, $P<0.001$) for patients with bipolar disorder than their counterparts in the comparison cohort. We conclude that patients with bipolar disorder had increased risk of developing gout even after adjusting for possible confounding factors.

1. Introduction

Metabolic abnormalities are more prevalent in patients with bipolar disorder than the general populations of both Western and Eastern countries. According to different criteria of metabolic syndrome, the prevalence ranged from 22.4% to 32.0%, nearly one to two times larger compared to the general adult population (Fagiolini et al., 2002; Fagiolini et al., 2005; Ford et al., 2002; Garcia-Portilla et al., 2008; Salvi et al., 2008; Sanisoglu et al., 2006; Yumru et al., 2007). Metabolic syndrome has been associated with increased risk of diabetes, heart disease, myocardial infarction, and stroke, as well as cardiovascular (Hu et al., 2004; Isomaa et al., 2001) and all-cause mortality (Lakka et al., 2002). For example, hyperglycemia, dyslipidemia, and obesity have been linked with bipolar disorder and may influence both quality of life and the course of bipolar disorder (Kolotkin et al., 2006; Thompson et al., 2006). However, uric acid, the final product of purine nucleotides metabolism, having been reported as a marker of increased cardiovascular risk (Taylor and MacQueen, 2006), has not been adequately studied in bipolar disorder.

Before the established treatment of bipolar disorder was developed, lithium had been used for treatment of gout. Allopurinol, which inhibits the production of uric acid, had been successfully used therapeutically as an adjuvant to lithium for treating bipolar patients (Akhondzadeh et al., 2006; Machado-Vieira et al., 2001; Machado-Vieira et al., 2008). Accordingly, it was hypothesized that gout and bipolar disorder may share similar pathophysiological mechanisms, e.g., purinergic dysfunction. (Anumonye et al., 1968; Machado-Vieira et al., 2002). Moreover, previous studies proposed that bipolar disorder was associated with a changed immune system (Ortiz-Domínguez et al., 2007; Ruggiero et al., 2006; Tsai et al., 2001a). Therefore, bipolar disorder and gout may share common pathogenesis, such as altered levels of tumor necrosis factor-alpha (TNF-α), interleukin-2 (IL-2), IL-1, and IL-6.

Furthermore, it is suggested that genetic, environmental, and lifestyle factors, including psychotropic medication (Bowden et al., 2000; Garcia-Portilla et al., 2008; Van Winkel et al., 2008), and smoking and substance abuse may play important roles in metabolic syndrome among bipolar patients. Similarly, hyperuricemia was also proposed to be associated with obesity, insulin resistance, hypertension, and alcohol use (Johnson et al., 2003). However, no study, according to our knowledge, has attempted to explore the association between bipolar disorder and the risk of gout.

Therefore, the purpose of this present retrospective follow-up study was to explore the association between bipolar disorder and the risk of gout using a nationwide population-based dataset. We

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hypothesize that patients with bipolar disorder may have higher risk of developing gout than the general population.

2. Methods

2.1. Database

This study used 1996–2006 data from the National Health Insurance Research Database (NHIRD). The dataset includes all claims data from the National Health Insurance (NHI) program. Taiwan initiated the NHI program in March 1995 as a means of financing healthcare for all citizens, and the NHI program currently has over 21 million enrollees, representing around 96% of the island's population. The NHI program is characterized by a single-payer payment system with unrestricted access to any mental healthcare provider of the patient's choice. Therefore, the NHRID is probably one of the largest and most comprehensive nationwide population-based data sources currently available anywhere, and offers a unique opportunity to identify the risk of developing gout among patients with bipolar disorder.

2.2. Study sample

This study consisted of the study cohort and comparison cohort. The study cohort comprised of all patients over the age of 18 years who had ever visited the outpatients departments for the treatment of bipolar disorder (International Classification of Diseases (ICD)-9-CM code of 296.0X, 296.4X, 296.5X, 296.6X, 296.7X, 296.80 or 296.89) between January and December 2000. We excluded those patients who had been diagnosed for bipolar disorder or any type of psychiatric disorders during the previous 4-year period in order to avoid the potential confounding factors of institutionalization and chronicity and to ensure the validity of diagnoses. Therefore, our sampled patients were newly diagnosed cases or in full remission. In addition, patients who had previously been diagnosed as gout (ICD-9-CM code of 274.XX) were excluded. Ultimately, there were 24,262 patients in the study cohort.

The comparison cohort was selected from an NHIRD sub-dataset including 1,073,891 randomly selected subjects, about 5% of all enrollees in the NHI program. There were no statistically significant differences in age, gender, and cost between the sample group in this sub-dataset and all enrollees. We excluded subjects in the sub-dataset if they had been diagnosed as having any type of psychiatric disorder or gout during the period of 1995–1999. We then selected our comparison cohort from this sub-dataset by randomly selecting 121,310 enrollees (five for every bipolar disorder patient) matched with the study group in terms of age (<25, 25–34, 35–44, 45–64, 65–74, >74), gender and the date of outpatient visits for the first bipolar disorder diagnosis.

Each patient was tracked 6 years from their index outpatient visits in 2000 until 2006 to identify all whether they had developed gout. In addition, to calculate the gout-free survival time after index outpatient visits over a 6-year period, the data were linked to the Taiwan death certificate data, with cases censored if individuals died during that time (6854 patients died including 2002 in the study cohort and 4852 in the comparison cohort).

2.3. Statistical analysis

The SAS statistical package (SAS System for Windows, Version 8.2) was used to perform the statistical analyses. Chi-square tests were performed to examine the differences between the two cohorts, in terms of demographic characteristics and comorbid medical disorders. Demographic characteristics included age, gender, monthly income, and geographical region. Comorbid medical disorders including hypertension, diabetes, hyperlipidemia, ischemic heart disease, and renal disease were recognized from claim data at the time of the index outpatient visits because they may increase the risk of developing gout.

We then estimated the 6-year gout-free survival rate using the log-rank test to examine the differences in the risk of developing gout between the two cohorts. Cox proportional hazard regressions were then performed to compute the 6-year survival rate, adjusting for other variables. Finally, we present hazard ratios (HR) along with 95% confidence intervals (CI). The differences were considered significant if a two-sided P value was ≤ 0.05.

3. Results

Table 1 describes the distribution of the demographic characteristics and comorbid medical disorders for these two cohorts. As the table shows, as compared to those patients in comparison cohort, patients with bipolar disorder were more likely to have no income ($P<0.001$), reside in the northern part of Taiwan ($P<0.001$) and cormobid with metabolic syndrome ($P<0.001$), renal disease ($P<0.001$), ischemic heart disease ($P<0.001$), and alcohol or substance dependence ($P<0.001$) at the time of the index outpatient visits.

Table 2 provides details for the 6-year follow-up period on the likelihood of developing gout for the two cohorts, with gout having occurred among 16.4% of the patients with bipolar disorder, and 13.6% of the patients in comparison cohort between 2000 and 2006 ($P<0.001$). The log-rank test indicated that patients with bipolar disorder had significantly lower 6-year gout-free survival rates than patients in comparison cohort ($P<0.001$). Table 2 also shows the crude hazard ratio indicating that, as compared to patients in the comparison cohort, the likelihood of developing gout during the follow-up period was 1.247 times (95% CI = 1.200–1.295) as great for patients with bipolar disorder.

Table 3 presents the details on the unadjusted and adjusted odds ratio of the development of gout by cohort. As the table shows, after adjusting for demographic characteristics, comorbid medical disorders, and substance or alcohol dependence, patients with bipolar disorder are 1.19 times (95% CI = 1.09–1.18, $P<0.001$) more likely to develop gout during the follow-up period than their counterparts in the comparison cohort. Furthermore, as expected, there was a greater likelihood of developing gout among those patients comorbid with metabolic syndrome, renal disease (HR = 1.81; 95% CI = 1.74–1.89, $P<0.001$), ischemic heart disease (HR = 1.29; 95% CI = 1.24–1.33, $P<0.001$), and alcohol or substance dependence (HR = 1.53; 95% CI = 1.32–1.78, $P<0.001$).

4. Discussion

To the best of our knowledge, this is the first study to address the association between bipolar disorder and the risk of gout using a nationwide population with a follow-up study design. Consistent with our hypothesis, patients with bipolar disorder demonstrate 1.14-fold higher risk of developing gout than the general population within the 6 years of follow-up period, after adjusting for demographic characteristics, comorbid medical disorders, and substance or alcohol dependence. Besides, in line with findings in previous studies, we also find that those who have metabolic syndrome, renal disease, ischemic heart disease, and alcohol or substance dependence tend to develop gout.

One possible explanation for the increased risk to develop gout among bipolar patients is that, those who suffer from bipolar disorder have purinergic dysfunction, and evolve into gout thereafter. The common pathophysiological mechanism of gout and bipolar disorder was supported by previous researches (Anumonye et al., 1968; Machado-Vieira et al., 2002). Additionally, among patients with bipolar disorder, altered immune system, such as specific phasic pattern manic/depressive or state-dependent acute/remitted immune activation, which was associated with altered level of TNF-α, IL-2, IL-1, IL-6, has been reported (Ortiz-Domínguez et al., 2007; Tsai et al., 2001b). With regard to gout, the innate immune inflammatory reaction is involved in the pathogenesis, which is characterized by direct promotion of uric acid crystals. It is thought to be mediated via stimulating cells via Toll-like receptor signaling and providing a surface for cleavage of C5 and formation of complement membrane attack complex (C5b-9), culminating in secretion of cytokines and other inflammatory mediators with an intense influx of neutrophils into the joint (Cronstein and Terkeltaub, 2006). For example, inflammatory markers, including white blood cell count, blood neutrophil count, C-reactive protein, and cytokines such as TNF-α, IL-2, IL-1, and IL-6 were found to be increased in patients with gout (Ruggiero et al., 2006). Consequently, it is suggested that immune activation in bipolar patients may lead to gout predisposition, which is related to the inflammatory reaction provoked by uric acid crystals followed by a cascade of immune response and is characterized by altered levels of TNF-α, IL-2, IL-1, and IL-6 (Ruggiero et al., 2006; Ortiz-Domínguez et al., 2007; Tsai et al., 2001b).

Gout shares metabolic risk factors (such as obesity, hypertension, and high levels of triglycerides) with certain diseases, including diabetes, renal disease, atherosclerosis, and heart disease (Johnson et al., 2003). Patients with bipolar disorder are prone to develop metabolic syndrome and then increase the risk of gout through few possible mechanisms. Hyperuricemia has been known to be the result of decreased renal uric acid excretion, which may be mediated by enhanced proximal tubular

Table 1
Demographic characteristics and comorbid medical disorders of patients with bipolar disorder and comparison group in Taiwan, 2000 ($n = 145,572$).

Variable	Patients with bipolar disorder		Comparison group		*P* value
	n	%	*n*	%	
Gender					1.000
Male	9548	39.4	47,740	39.4	
Female	14,714	60.7	73,570	60.7	
Age					1.000
<25	2540	10.5	12,700	10.5	
25–34	4632	19.1	23,160	19.1	
35–44	5361	22.1	26,805	22.1	
45–64	7370	30.4	36,850	30.4	
65–74	2667	11.0	13,335	11.0	
>74	1692	7.0	8460	7.0	
Metabolic syndrome					<0.001
Hypertension, diabetes and hyperlipidemia	2525	10.4	8970	7.4	
Hypertension and diabetes	1436	5.9	5012	4.1	
Hypertension and hyperlipidemia	1959	8.1	8610	7.1	
Hyperlipidemia and diabetes	931	3.8	3351	2.8	
Hypertension	3579	14.8	15,727	13.0	
Diabetes	1012	4.2	3110	2.6	
Hyperlipidemia	1595	6.6	7194	5.9	
None	11,225	46.3	69,336	57.2	
Renal disease					<0.001
Yes	2790	11.5	10,067	8.3	
No	21,472	88.5	111,243	91.7	
Ischemic heart disease					<0.001
Yes	6456	26.6	10,067	8.3	
No	17,806	73.4	111,243	91.7	
Monthly income					<0.001
0	14,745	60.8	47,949	39.5	
NT$1–15,840	5974	24.6	32,055	26.4	
NT$15,841–25,000	2769	11.4	29,345	24.2	
≥NT$25,001	774	3.2	11,960	9.9	
Metabolic syndrome					<0.001
Hypertension, diabetes and hyperlipidemia	2525	10.4	8970	7.4	
Hypertension and diabetes	1436	5.9	5012	4.1	
Hypertension and hyperlipidemia	1959	8.1	8610	7.1	
Hyperlipidemia and diabetes	931	3.8	3351	2.8	
Geographic region					<0.001
Northern	16,073	66.2	72,634	59.9	
Central	6111	25.2	27,156	22.4	
Southern	1801	7.4	19,696	16.2	
Eastern	277	1.1	1824	1.5	
Alcohol or substance dependence					<0.001
Yes	1202	5.0	35	0.0	
No	23,060	95.0	121,275	100.0	

sodium reabsorption and hyperinsulinemia (Puig and Martinez, 2008). High prevalence of metabolic syndrome in patients with bipolar disorder (Ford et al., 2002; Garcia-Portilla et al., 2008; Yumru et al., 2007) could partially explain the impact of hyperinsulinemia on the development of hyperuricemia and gout. Furthermore, medication used in bipolar disorder, either antipsychotics, especially second-generation antipsychotics, or mood stabilizer, such as valproic acid or lithium, may also increase the occurrence of metabolic syndrome (Garcia-Portilla et al., 2008; Van Winkel et al., 2008).

Considering the relationship between lifestyle and gout, maintaining a healthy lifestyle and dietary recommendation is crucial (Becker and Chohan, 2008) and needs sufficient cognitive ability in the prevention and management of gout. Bipolar disorder is often associated with cognitive deficits, such as in executive functioning, episodic memory, sustained concentration, and visuospatial skills (Osuji and Cullum, 2005). Moreover, the cognitive deficits tend to be

Table 2
Crude hazard ratio of developing gout during 6-year follow-up period for sampled patients with bipolar disorder and comparison group in Taiwan ($n = 145,572$).

Variable	Patients with bipolar disorder		Comparison group	
	Total no.	%	Total no.	%
Developing gout				
Yes	3976	16.4	16,482	13.6
No	20,286	83.6	104,828	86.4
Crude HR, 95% CI	1.247 (1.200–1.295)		1.000	

Note: HR = hazard ratio; CI = confidence interval.

Table 3
Adjusted hazard ratio of developing gout during 6-year follow-up period for sampled patients with bipolar disorder and comparison group in Taiwan ($n = 145,572$).

Variables	Developing gout	
	Unadjusted HR	Adjusted HR[a]
	95% CI	95% CI
Cohort		
Bipolar disorder	1.25*** (1.20–1.30)	1.19*** (1.09–1.18)
Comparison group (reference group)	1.00	1.00
Gender		
Male	1.94*** (1.88–1.99)	2.20*** (1.23–2.27)
Female (reference group)	1.00	1.00
Age		
<25 (reference group)	1.00	1.00
25–34	1.75*** (1.62–1.90)	1.40*** (1.29–1.53)
35–44	2.63*** (2.44–2.84)	1.54*** (1.42–1.67)
45–64	4.65*** (4.33–5.00)	1.74*** (1.60–1.88)
65–74	6.67*** (6.18–7.20)	1.82*** (1.67–1.98)
>74	5.80*** (5.32–6.27)	1.66*** (1.51–1.82)
Geographic location		
Northern (reference group)	1.00	1.00
Central	1.00 (0.96–1.06)	1.00 (0.95–1.05)
Southern	0.95* (0.91–0.99)	0.89*** (0.85–0.93)
Eastern	1.15 (1.02–1.29)	1.02 (0.90–1.16)
Monthly income		
0 (reference group)	1.00	1.00
NT$1–15,840	1.01 (0.96–1.06)	1.03 (0.97–1.09)
NT$15,841–25,000	1.20** (1.16–2.24)	1.06** (1.02–1.11)
≥NT$25,001	1.11** (1.05–1.17)	1.02 (0.96–1.08)
Metabolic syndrome		
Hypertension, diabetes and hyperlipidemia	10.09*** (9.61–10.60)	8.04 (7.61–8.49)
Hypertension and diabetes	4.59*** (4.29–4.91)	3.39*** (3.16–3.64)
Hypertension and hyperlipidemia	8.75*** (8.31–9.20)	7.15*** (6.77–7.55)
Hyperlipidemia and diabetes	7.45*** (6.92–7.99)	6.57*** (6.11–7.06)
Hypertension	3.19*** (3.04–3.35)	2.56*** (2.43–2.70)
Diabetes	2.76*** (2.51–3.03)	2.38*** (2.17–2.61)
Hyperlipidemia	5.92*** (5.60–6.27)	5.70*** (5.39–6.03)
None (reference group)	1.00	1.00
Renal disease		
Yes	3.10*** (2.97–3.22)	1.81*** (1.74–1.89)
No (reference group)	1.00	1.00
Ischemic heart disease		
Yes	2.94*** (2.85–3.04)	1.29*** (1.24–1.33)
No (reference group)	1.00	1.00
Alcohol or substance dependence		
Yes	1.84*** (1.61–2.11)	1.53*** (1.32–1.78)
No (reference group)	1.00	1.00

[a] Adjusted for patient's gender, age, monthly income and geographical region, metabolic syndrome, ischemic heart disease, renal disease, and alcohol or substance dependence.

* $P<0.05$.

** $P<0.01$.

*** $P<0.001$.

present regardless of mood state, even in remitted patients, neuropsychological deficits related to attention/processing speed, memory, and particularly to executive function could be found (Robinson et al., 2006). Accordingly, impaired cognitive function in bipolar patients may result in inadequate ability to maintain a healthy lifestyle and increase the risk of gout.

Rates of substance abuse are high in bipolar disorder (Goodwin and Jamison, 1990). Most reporting estimates of comorbid lifetime alcohol abuse were 30% or greater (Cassidy et al., 2001). Previous studies showed that high risk of gout attack was related to increased alcohol consumption and that this risk varied according to the type of alcoholic beverage consumed (Lin et al., 2000; Zhang et al., 2006), and even a light-to-moderate amount could trigger recurrent gout attacks (Zhang et al., 2006). Increased urate generation and decreased urate excretion were proposed to induce gout attack in individuals with increased alcohol consumption (Johnson et al., 2003), as seen in patients with bipolar disorder.

A number of limitations should be considered to interpret this study. First of all, this study using nationwide population-based dataset was conducted in an Asian population, so the results may not be generalizable to other ethnic groups. Second, despite the statistics being as accurate and comprehensive as possible in Taiwan, misclassification of disease within the registry system may serve to confound the results. Third, some variables such as psychotropic medications, dietary habits, cigarette smoking habits, and body mass indices, which may contribute to gout development, were not included in our analysis because of a lack of dataset information; however, given that this study was based on a large-scale population in Taiwan and featured a follow-up design, it is a worthy model representing a naturalistic disease course and nationwide public concern. Finally, our sampled patients were newly diagnosed cases or in full remission. These patients may be less severe or have less treatment exposure than those excluded.

In conclusion, this study finds increased risk of developing gout among patients with bipolar disorder, even controlling for demographic characteristics, comorbid medical disorders, and substance or alcohol dependence. The results of this study should alert clinicians to assess and monitor the presence of metabolic abnormalities including hypeurecemia and gout in bipolar patients. Early identification and intervention by the psychiatric teams to prevent from developing gout and subsequent consequences should be included in the treatment plans.

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