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Research report

Increased risk of developing stroke among patients with bipolar disorder after an acute mood episode: A six-year follow-up study

Herng-Ching Lin [a], Shang-Ying Tsai [b,c], Hsin-Chien Lee [b,c,*]

[a] *School of Health Care Administration, Taipei Medical University, Taipei, Taiwan*
[b] *Department of Psychiatry, Taipei Medical University Hospital, 252 Wu-Hsing St., Taipei 110, Taiwan*
[c] *Department of Psychiatry, School of Medicine, Taipei Medical University, Taipei, Taiwan*

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Abstract

Background: Despite cerebrovascular diseases having been reported as one of the major causes of death among patients with bipolar disorder, there is scant information on the risk of stroke among this patient population. This study estimated the relative risk of developing stroke among patients with bipolar disorder in 6 years following hospitalization for an acute mood episode compared with patients undergoing appendectomy.
Methods: Two study cohorts were identified from the Taiwan National Health Insurance Research Database for the year 1998: patients hospitalized with bipolar disorder, and patients undergoing an appendectomy. Follow-up was undertaken to determine whether sampled patients had utilized emergency medical services for the management of any type of stroke in the period 1998–2003.
Results: Stroke occurred among 2.97% of patients with bipolar disorder and 1.50% of patients undergoing appendectomy between 1998 and 2003. The adjusted odds ratio of developing stroke, by cohort, shows that after adjusting for demographic characteristics, comorbid medical disorder, and substance or alcohol dependence, patients with bipolar disorder were more likely to develop stroke (OR=2.05; 95% CI=1.73–3.54).
Limitations: The validity of diagnoses, lacking of information on smoking, body mass index, and socioeconomic status, and possible selection bias might compromise the findings.
Conclusions: During the six-year follow-up period, the likelihood of developing stroke was twice as great amongst patients with bipolar disorder as patients undergoing an appendectomy. A requirement exists for the initiation of research providing an understanding of the pathophysiological mechanisms of the association between stroke and bipolar disorder.

Keywords: Bipolar disorder; Stroke; Case-control studies

1. Introduction

As a major psychiatric disorder characterized by fluctuations between depression and mania, bipolar disorder is a devastating condition with severe economic and social impacts (Simon, 2003). The lines of evidence suggest that in addition to the psychiatric symptoms and attendant dysfunction, bipolar disorder is associated

* Corresponding author. Department of Psychiatry, Taipei Medical University Hospital, 252 Wu-Hsing St., Taipei 110, Taiwan. Tel.: +886 2 2737 2181x3667; fax: +886 2 2378 9788.
E-mail address: ellalee@tmu.edu.tw (H.-C. Lee).

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with several medical conditions leading to substantial morbidity and mortality (Osby et al., 2001; Angst et al., 2002). As a result of the increasing medical burden in the healthcare of patients with bipolar disorder, it has now become a matter of some urgency to gain a greater understanding of this condition (Kupfer, 2005).

Within the studies focusing on medical illnesses among patients with bipolar disorder, the most common medical problems cited are obesity, diabetes mellitus and subsequent cardiovascular disease; all of these medical conditions, as well as depressive symptoms, are recognized as risk factors for stroke (Everson et al., 1998; Krishnan, 2005). Thus, there would appear to be a biologically plausible association between bipolar disorder and stroke.

Nevertheless, there is scant information on the risk of developing stroke among patients with bipolar disorder, despite cerebrovascular diseases having been reported as one of the major causes of death among this particular patient population (Hoyer et al., 2000; Joukamaa et al., 2001; Tsai et al., 2005). Indeed, there has been only one prior study, undertaken by Nilsson and Kessing (2004), which used a Danish registry dataset to estimate the risk, among patients previously discharged with affective disorder, of receiving a stroke diagnosis. They could not find any association between manic/bipolar disorder and stroke.

The aim of the present study is to estimate the risk of developing stroke among patients with bipolar disorder in 6 years following hospitalization for an acute mood episode, as compared to another cohort of patients undergoing an appendectomy during the same period. Patients were identified from a nationwide population-based dataset provided by the Taiwan National Health Insurance Research Database (NHIRD) for the year 1998, with follow-up being carried out until the end of 2003. The risks of developing stroke for these two cohorts were subsequently calculated and compared after adjusting for demographic characteristics and co-morbid medical conditions.

2. Methods

2.1. Database

This study used administrative claims data from the NHIRD, published by the National Health Research Institute in Taiwan, covering the years 1998 to 2003. The dataset includes all claims data from the National Health Insurance (NHI) program, a program implemented in Taiwan in March 1995 as a means of financing healthcare for all Taiwanese citizens. The NHI program currently has over 21 million enrollees, representing around 96% of the island's population, and is characterized by a single-payer payment system with unrestricted access to any mental healthcare provider of the patient's choice. Thus, the NHRID is possibly the largest and most comprehensive population-based data source currently available anywhere, and offers a unique opportunity to identify the risk of developing stroke amongst patients with bipolar disorder.

3. Study sample

Our two study cohorts comprised of (i) all patients, aged 18 or over, hospitalized for bipolar disorder, with an ICD-9-CM code of 296.0X, 296.4X, 296.5X, 296.6X, 296.7X, 296.80 or 296.89 as the primary diagnosis between January and December 1998; and (ii) all patients aged 18 or over hospitalized for an appendectomy, with an ICD-OP code of 47.0 as the primary operative procedure over the same period. Patients undergoing an appendectomy were excluded if they had been diagnosed as having any major psychiatric disorder (ICD-9-CM codes 290, 294, 295, 296 or 297). Ultimately, 18,702 eligible patients were selected for this study, 2289 with bipolar disorder and 16,413 undergoing an appendectomy.

The reason for the selection of those patients who had undergone an appendectomy as the control group was that they were relatively indistinguishable from the general population; indeed, there were no statistically-significant differences found between the control cohort and the general population with regard to either gender or age. Furthermore, to the best of our knowledge, the procedures involved in an appendectomy have no known long-term impacts on brain functioning, and indeed, there has never been any study reporting any increased risk of bipolar disorders among patients undergoing an appendectomy.

Follow-up of these two study cohorts was subsequently undertaken until the end of 2003 in order to determine whether any of sampled patients had utilized emergency medical services for the management of any type of stroke (ICD-9-CM codes 430–438). Since a substantial number of stroke victims do not survive beyond their visit to the emergency department, the utilization of emergency department services, rather than the consumption of inpatient care, may better reflect the actual scenario of stroke incidence.

4. Statistical analysis

The SAS statistical package (SAS System for Windows, Version 8.2) was used to perform the statistical

Table 1
Demographic characteristics and comorbid medical disorders of sampled patients with bipolar disorder and undergoing an appendectomy in Taiwan, 1998 (n=18,702)

Variable	Patients with bipolar disorder		Patients undergoing appendectomy		P value
	Total no.	%	Total no.	%	
Gender					0.006
Male	1075	47.0	82,171	50.1	
Female	1214	53.0	8196	49.9	
Age					
<45	1608	70.3	11,888	72.4	<0.001
45–64	513	22.4	3054	18.6	
65–74	131	5.7	1042	6.4	
>74	37	1.6	429	2.6	
Hypertension					<0.001
Yes	105	4.6	359	2.2	
No	2184	95.4	16,054	97.8	
Diabetes					<0.001
Yes	101	4.4	363	2.2	
No	2188	95.6	16,050	97.8	
Hyperlipidemia					<0.001
Yes	20	0.9	48	0.3	
No	2269	99.1	16,365	99.7	
COPD					0.035
Yes	23	1.0	102	0.6	
No	2266	99.0	16,311	99.4	
Renal disease					<0.001
Yes	72	3.1	76	0.5	
No	2217	96.9	16,337	99.5	
Alcohol dependence					<0.001
Yes	28	1.2	10	0.0	
No	2261	98.8	16,403	100.0	
Substance dependence					
Yes	16	0.7	6	0.0	<0.001
No	2273	99.3	16,407	100.0	

analyses. Descriptive statistical analyses, including frequency and percentage, were performed on all of the identified variables, with Chi-square tests also being used to examine the differences between the two cohorts, in terms of demographic characteristics, comorbid medical disorders, and alcohol or substance dependence. Demographic characteristics included age, gender and geographical region, with patient age being categorized into one of the four groups, <45, 45–64, 65–74 and >74 years. The geographical region within which patients were located was also taken into consideration since geographical variations in the incidence of strokes has been demonstrated in a prior study (Engstrom et al., 2001). Comorbid medical disorders including hypertension, diabetes, hyperlipidemia, chronic obstructive pulmonary disease (COPD) or renal disease were recognized from claim data at the time of the index discharge because they might increase the risk of developing stroke.

The multiple logistic regression analyses were employed in order to compare calculations, between these two study cohorts, of the crude and adjusted odds ratio of developing stroke after the index discharge. Our analysis provides adjustment for patient demographic characteristics, comorbid medical disorders, and alcohol or substance dependence. A significance level of $p<0.05$ was adopted for this study.

5. Results

The results show that the median age for those patients with bipolar disorder was 36 years (interquartile range, 28–47 years), while the median age for those patients undergoing an appendectomy was 34 years (interquartile range, 26–46 years). 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 undergoing an appendectomy, patients with bipolar disorder were more likely to be female and comorbid with hypertension ($p<0.001$), diabetes ($p<0.001$), hyperlipidemia ($p<0.001$), COPD ($p=0.035$), renal disease ($p<0.001$), alcohol dependence ($p<0.001$) or substance dependence ($p<0.001$) at the time of the index discharge.

Table 2 provides details for the six-year follow-up period on the likelihood of developing stroke for the two cohorts, with stroke having occurred among 2.97% of the patients with bipolar disorder, and 1.50% of the patients undergoing an appendectomy between 1998 and 2003 ($p<0.001$). The crude odds ratio indicates that, as compared to patients undergoing an appendectomy, the likelihood of developing stroke during the follow-up period was twice as great for patients with bipolar disorder.

Details on the adjusted odds ratio of the development of stroke, by cohort, are presented in Table 3. As the table shows, after adjusting for demographic characteristics, comorbid medical disorders, and substance or

Table 2
Crude odds ratio of developing stroke during six-year follow-up period for sampled patients with bipolar disorder and undergoing an appendectomy in Taiwan (n=18,702)

Variable	Patients with bipolar disorder		Patients undergoing appendectomy	
	Total no.	%	Total no.	%
Developing stroke				
Yes	69	2.97	246	1.50
No	2221	97.93	16,166	98.50
Crude OR	2.00		1.00	
95% CI	1.53–2.63		–	

Table 3
Adjusted odds ratio of developing stroke during six-year follow-up period for sampled patients with bipolar disorder and undergoing an appendectomy in Taiwan (n=18,702)

Variables	Developing stroke		
	OR	95% CI	p value
Cohort			
Bipolar disorder	2.05	1.73–3.54	<0.001
Appendectomy (reference group)	1.00		
Gender			
Male	1.48	1.17–1.87	0.001
Female (reference group)	1.00		
Age			
<45 (reference group)	1.00		
45–64	7.06	5.10–9.78	<0.001
65–74	14.99	10.49–21.42	<0.001
>74	26.19	17.51–39.18	<0.001
Geographic location			
Northern (reference group)			
Central	1.05	0.77–1.44	0.743
Southern	1.31	1.00–1.70	0.049
Eastern	1.88	1.03–3.44	0.039
Hypertension			
Yes	1.89	1.32–2.69	<0.001
Diabetes			
Yes	2.48	1.73–3.58	<0.001
Hyperlipidemia			
Yes	0.65	0.08–5.09	0.697
COPD			
Yes	1.09	0.51–2.33	0.817
Renal disease			
Yes	0.57	0.17–1.85	0.347
Alcohol dependence			
Yes	3.42	1.21–9.22	<0.001
Substance dependence			
Yes	8.69	1.06–71.06	0.044

alcohol dependence, sampled patients with bipolar disorder were more likely to develop stroke during the follow-up period than their counterparts undergoing an appendectomy (OR=2.05; 95% CI=1.73–3.54). Furthermore, as expected, there was a greater likelihood of the development of stroke among those patients comorbid with hypertension (OR=1.89; 95% CI=1.32–2.69) and diabetes (OR=2.48; 95% CI=1.73–3.58).

6. Discussion

To the best of our knowledge, our study represents the first attempt to investigate the risk of developing stroke among patients with bipolar disorder in 6 years following hospitalization for an acute mood episode, after adjusting for patient's demographic characteristics, comorbid medical disorders, and substance or alcohol dependence. We find that the likelihood of the development of stroke during the six-year follow-up period was twice as great among patients with bipolar disorder as compared to their counterparts who had undergone an appendectomy. The findings of this study contradict the observations reported in the prior study by Nilsson and Kessing (2004); nonetheless, patients with affective disorder in their study were categorized in accordance with the ongoing episode at the time of their referral, as patients suffering from either depression or mania. Those patients in the depression group who were found to have an increased risk of developing stroke may actually have been cases of bipolar disorder with a depressive episode. A further reason for the discrepancy could actually arise from the control cohort, since patients with osteoarthritis may have been taking non-steroidal anti-inflammatory drugs (NSAIDs) which would of course have some influence on the risk of developing stroke (Qureshi et al., 2001; Qureshi, 2003).

The actual mechanisms contributing to the association between bipolar disorder and the subsequent development of stroke remain unclear. An unhealthy lifestyle, comorbid medical conditions, and the use of psychotropic medications could all contribute to the increased risk of stroke among patients with bipolar disorder; however, they could also be at an increased risk of stroke as a result of their existing brain vulnerability. A number of prior neuroimaging studies have consistently reported structural brain abnormalities among patients with bipolar disorder (Drevets et al., 1997; Adler et al., 2005; Lyoo et al., 2006). The neuroanatomical deficits may well be present in the early stages of bipolar disorder and may become aggravated as the disease progresses (Kaur et al., 2005).

Enhanced platelet activity and hypercoagulability have been reported to be associated with depression (Nemeroff and Musselman, 2000; von Kanel et al., 2001). These alterations in hemostatic function may contribute to the development of stroke among patients with bipolar disorder. Besides, studies indicate activation of inflammatory response system in patients with bipolar disorder (Tsai et al., 1999; Tsai et al., 2001). The elevation of certain proinflammatory cytokines may play an important role in the pathogenesis of stroke (Arumugam et al., 2005).

Furthermore, it is possible that bipolar disorder may share a common etiology with stroke, with recent studies having suggested that glycogen synthase kinase-3 (GSK-3), an emerging therapeutic target for bipolar disorder, could be a crucial element in the pathogenesis of atherothrombosis (Gould et al., 2004; Eto et al., 2005). The close relationship between bipolar disorder and stroke indicates the urgent need for the integration of

psychiatry into the mainstream of medicine as a clinical neuroscience discipline (Insel and Quirion, 2005).

7. Limitations

A particular strength of this study is the use of a population-based dataset which enables us to trace all stroke incidents; nevertheless, this study still suffers from three limitations which should be addressed. First of all, the psychiatric and stroke diagnoses, which rely on administrative data reported by physicians or hospitals, may be less accurate than those made under a standardized schedule; however, the development of such a population-based dataset containing this sort of information would be extremely costly and difficult to achieve.

Secondly, there was no availability for use in this study of data on tobacco use, body mass index and socioeconomic status, all of which might influence the risk of developing stroke. Since a number of prior studies have observed a greater frequency of heavy smoking among psychiatric patients, there may even be some underestimation of the odds ratio of the development of stroke among patients with bipolar disorder.

Thirdly, the sample of patients bipolar disorder used in this study was based upon acute mood episodes which occurred during the first year of the study period; as such, they may not be a truly representative cohort of all patients with bipolar disorder since symptom-free patients would have been excluded from the study sample.

8. Conclusions

Despite these limitations, we have found that during the six-year follow-up period, the risk of developing stroke was about twice as great amongst patients with bipolar disorder, as compared patients undergoing an appendectomy, and that this association was totally independent of any initial comorbid hypertension, diabetes, hyperlipidemia and alcohol or substance dependence.

We believe that there is an urgent requirement for the initiation of research aimed at gaining a better understanding of the underlying pathophysiological mechanisms of stroke and their association with bipolar disorder. The findings of this study may also fill the knowledge gap with regard to the comorbidity of bipolar disorder with other medical illnesses, reflecting the fact that the treatment of bipolar disorder has traditionally been segregated from general medical care.

In order to prevent any adverse outcomes, practicing psychiatrists and other mental healthcare professionals must be aware of the increased risk of the development of stroke among patients with bipolar disorder and encouraged to be with the ultimate aim of providing more integrated intervention.

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