

Increased Risk of Stroke in Patients With Bullous Pemphigoid

A Population-Based Follow-Up Study

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Background and Purpose—Although previous research reveals that cardiovascular events and thromboembolic diseases are important causes of death in patients with bullous pemphigoid (BP), the risk of stroke after the diagnosis of BP relative to the general population remains unknown. Using a randomly selected nationwide population-based sample, this study investigates the risk of stroke in patients with BP compared with unaffected individuals of a similar age.

Methods—This study analyzes data from Taiwan's National Health Insurance Research Database. This sample included 390 patients with BP and 1950 matched subjects as a comparison group. Stratified Cox proportional hazard regressions were used to calculate the 3-year stroke risk for these 2 groups after adjusting for patient's age, sex, and comorbid medical disorders at baseline.

Results—Of the 2340 patients in the sample, 312 patients (13.3%) had strokes during the 3-year follow-up period, 89 (22.8% of the patients with BP) in the study group and 223 (11.4% of patients without BP) in the comparison group ($P < 0.001$). The hazard ratio for stroke for patients with BP was 2.37 (95% CI, 1.78 to 3.15; $P < 0.001$) times as high that for patients without BP within the 3-year follow-up period after adjusting for hypertension, diabetes, hyperlipidemia, heart failure, atrial fibrillation, and coronary heart disease.

Conclusions—Patients with BP have an increased risk of stroke and particularly ischemic stroke. (*Stroke*. 2011;42:319-323.)

Key Words: bullous pemphigoid ■ epidemiology ■ stroke

Bullous pemphigoid (BP) is the most common autoimmune blistering disease occurring in the elderly population.^{1,2} Immunologic indicators of BP include the presence of IgG autoantibodies. These antibodies target proteins in the keratinocyte hemidesmosome, a basal cell basement membrane adhesion structure, resulting in subepidermal blister formations.^{3,4} BP usually accompanies pruritic urticarial plaques and large tense bullae in the lower abdomen, inner and anterior thighs, and flexural areas.⁵ Histopathologic examination shows a picture of subepidermal bullae with eosinophils, and direct immunofluorescence studies on the perilesional skin or indirect immunofluorescence studies using the patient's serum can confirm the diagnosis of BP.^{6,7} Systemic and potent topical corticosteroids are the primary treatment of BP.⁸

Several studies indicate an increase in mortality rates after the diagnosis of BP. The 1-year mortality rate is between 19% and 41% in Europe and between 6% and 12% in the United States.^{9–12} Older age, a generally high prevalence of medical comorbidities in elderly people, and the immune-suppressed status caused by therapy may account for high mortality among patients with BP. However, the inflammatory process of bullous dermatosis itself may also play a role. BP is more

than just an autoimmune disease confined to skin; patients with BP have elevated serum levels of proinflammatory cytokines, soluble E-selectin, and vascular endothelial growth factor, indicating endothelial activation.^{13,14} The activation of luminal endothelium in BP can predispose patients to various vascular events, including stroke.^{15,16} Although previous case studies and observational studies reveal that, in addition to infection, cardiovascular events or thromboembolic diseases are important causes of death in patients with BP, the risk of stroke after the diagnosis of BP relative to the age-matched general population remains unknown.^{12,17}

The goal of this study is to investigate the risk of stroke in patients with BP compared with unaffected individuals of a similar age, adjusted for underlying comorbidities, using a randomly selected nationwide population-based sample.

Materials and Methods

Database

This study analyzes data from Taiwan's National Health Insurance Research Database (NHIRD) published by the National Health Research Institute, Taipei, Taiwan. Taiwan initiated the National Health Insurance (NHI) program in March 1995 to offer affordable

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health care for all residents. The NHI program, a single-payer system with the government as the sole insurer, provides universal medical coverage, comprehensive benefits, and access to any medical institution of the patient's choice. As of 2007, the NHIRD covered all inpatient and outpatient medical benefit claims for 22.60 million out of the total 22.96 million population of Taiwan, >98% coverage. The NHIRD database includes registries of contracted medical facilities, board-certified physicians, catastrophic illness patients and beneficiaries, monthly claims summaries for inpatient claims, ambulatory care claims, and details of inpatient orders and ambulatory care orders. The NHIRD data are generally accurate because the NHI Bureau regularly audits claims and imposes fines for false claims at the rate of 100 times the fraudulent claim. Hundreds of studies have been published based on these data.

Consultation with the chairman of the Institutional Review Board of Taipei Medical University confirmed that this study was exempt from full review by the Institutional Review Board because the NHIRD database in this study consists of deidentified secondary data released to the public for research purposes.

Study Sample

This study includes a study group and a comparison group. The study sample was drawn from the ambulatory care claims database that includes every physician consultation in clinics, primary care facilities, outpatient departments of hospitals, and emergency departments of hospitals in Taiwan. Specifically, the sample includes 1039 patients with a principal diagnosis of BP who visited ambulatory care centers (International Classification of Diseases, 9th Revision, Clinical Modification code 694.5, pemphigoid) between January 1, 2004, and December 31, 2004. Patients (n=260) who had been diagnosed with BP before 2004 were excluded from the sample to increase the likelihood of identifying only new cases. However, since Taiwan initiated the NHI program in 1995, it is not possible to track medical use trends before 1996 using the data set in this study. Therefore, it is not possible to isolate patients with BP before 1996. Patients' first ambulatory care visits for the treatment of BP in 2004 served as the index ambulatory care visit for this study. Patients with any type of stroke (International Classification of Diseases, 9th Revision, Clinical Modification codes 430 to 438) before their index ambulatory care visit (n=324) were excluded. In addition, patients who were <45 years old (n=65) were also excluded. Ultimately, the sample in this study comprised 390 patients with BP.

The comparison group was taken from the Longitudinal Health Insurance Database released by the National Health Research Institute. The Longitudinal Health Insurance Database contains the original claim data of 1 000 000 beneficiaries randomly sampled from the Registry for Beneficiaries of the NHIRD; the population for random sampling in this study included every beneficiary of the NHI Program during any period in 2005. There is no significant difference in the sex distribution, age distribution, or average insured payroll-related amount between the patients in the Longitudinal Health Insurance Database group and the original NHIRD group. The sample excluded patients who were <45 years old in 2004 or who had a history of stroke before 2004. Patients who were diagnosed with BP between 1996 and 2007 were also excluded. Thereafter, 1950 subjects (5 subjects for each BP patient) matching with the study group in terms of sex and age (as continuous variable) were randomly extracted from the remaining beneficiaries using the SAS statistical package (SAS System for Windows, Version 8.2). Patients' first ambulatory care visits in 2004 served as the index ambulatory care visit. The 2340 patients in this study were individually traced for 3 years after their index ambulatory care visits to identify patients who had a stroke during the follow-up period.

Statistical Analysis

We used the SAS statistical package to perform all statistical analyses in this study. Pearson χ^2 tests and *t* tests were used to test the differences in sociodemographic characteristics, including age, sex, and comorbidities at the time of the index ambulatory care. These comorbidities included hypertension, diabetes, hyperlipidemia, heart failure, atrial fibrillation, and coronary heart disease, and

Table 1. Patients With BP and the Comparison Group in Relation to Sociodemographic Characteristics in Taiwan, 2004 (n=2340)

Variables	Patients With BP (N=390)		Comparison Group (N=1950)		P
	No.	Percent	No.	Percent	
Age, mean years (SD)	72.5±12.5		72.5±12.5		1.000
Sex					1.000
Male	224	57.4	1120	57.4	
Female	166	42.6	830	42.6	
Heart failure					<0.001
Yes	22	5.6	41	2.1	
No	368	94.4	1909	97.9	
Atrial fibrillation					0.204
Yes	5	1.3	13	0.7	
No	385	98.7	1937	99.3	
Hypertension					0.132
Yes	119	30.5	672	34.5	
No	271	69.5	1278	65.5	
Coronary heart disease					0.674
Yes	37	9.5	172	8.8	
No	353	90.5	1778	91.2	
Diabetes					0.013
Yes	67	17.2	244	12.5	
No	323	82.8	1706	87.5	
Hyperlipidemia					0.120
Yes	20	5.1	68	3.5	
No	370	94.9	1882	96.5	

were extracted from the NHIRD because these conditions may exacerbate the risk of stroke for the study and comparison groups alike.

The Kaplan-Meier method was used to compare the 3-year stroke-free survival times with baseline variables at time 0. The log-rank test was performed to determine the differences in cumulative stroke-free survival rates between the study group and comparison group. Finally, stratified Cox proportional hazard regressions (stratified by sex and age) revealed the longitudinal hazard of stroke for both groups after adjusting for comorbid medical disorders at baseline. A 2-sided probability value ≤ 0.05 was significant.

Results

Table 1 compared the differences between the study group and the comparison group in terms of sociodemographic characteristics and comorbid medical disorders. The mean age for the sampled patients was 72.5 years (SD, 12.5). After matching groups for age and sex, Pearson χ^2 tests revealed that patients with BP were more likely to have comorbidities of heart failure ($P<0.001$) and diabetes ($P=0.013$) compared with patients without BP. The 2 groups were not significantly different in the prevalence of hypertension ($P=0.132$), hyperlipidemia ($P=0.120$), atrial fibrillation ($P=0.204$), or coronary heart disease ($P=0.674$).

Table 2 compares the distribution of stroke incidents during the 3-year follow-up period for patients with and without BP. Of the sample of 2340 patients, 312 patients (13.3%) had strokes during the 3-year follow-up period, 89

Table 2. Crude and Adjusted HRs for Stroke During the 3-Year Follow-Up Period for Patients With BP and Patients in the Comparison Group in Taiwan (n=2340)

Stroke	Total Sample		Comparison		BP	
	No.	Percent	No.	Percent	No.	Percent
Three-year follow-up period						
Yes	312	13.3	223	11.4	89	22.8
No	2028	86.7	1727	88.6	301	77.2
Crude HR (95% CI)	...		1.0		2.36† (1.79–3.13)	
Adjusted* HR (95% CI)	...		1.0		2.37† (1.78–3.15)	

*Stratified Cox proportional hazard regressions (stratified by sex and age) were performed to adjust for hypertension, diabetes, hyperlipidemia, heart failure, atrial fibrillation, and coronary heart disease.

† $P < 0.001$.

(22.8% of the patients with BP) in the study group and 223 (11.4% of patients without BP) in the comparison group ($P < 0.001$). The log-rank test shows a significant difference in stroke-free survival rates between patients with and without BP during the 3-year follow-up period (χ^2 : 41.048; $P < 0.001$). The Figure displays the survival times for both groups based on Kaplan-Meier survival analysis.

Table 2 also presents the crude and adjusted hazard ratios (HRs) of stroke within the 3-year follow-up periods after the index ambulatory care visits between patients with and without BP. These results show that compared with patients without BP, the crude HR for stroke for patients with BP during the 3-year follow-up period was 2.36 (95% CI, 1.79 to 3.13; $P < 0.001$). Compared with patients without BP, stratified Cox proportional hazard regressions (stratified by sex and age) revealed that the HR for stroke for patients with BP was 2.37 (95% CI, 1.78 to 3.15; $P < 0.001$) times as high within the 3-year follow-up period after adjusting for patient's

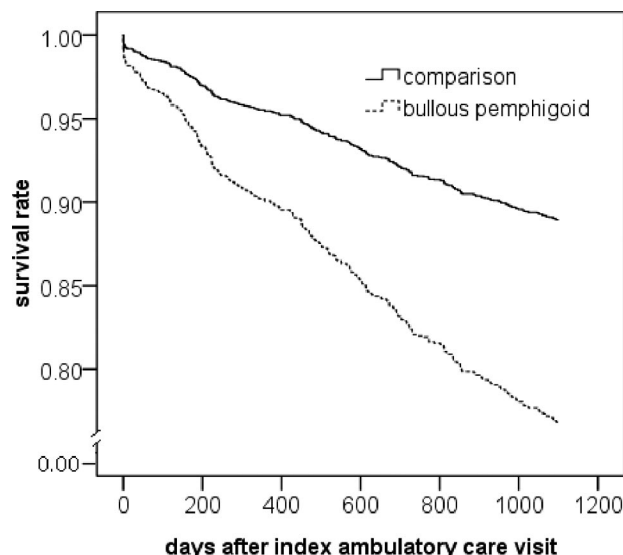


Figure. Three-year stroke-free survival rates for patients with BP and a comparison group in Taiwan, 2004.

age, sex, hypertension, diabetes, hyperlipidemia, heart failure, atrial fibrillation, and coronary heart disease.

Discussion

This study shows an approximately 2-fold increase in the incidence of stroke for patients with BP compared with the comparison group. The risk of stroke associated with BP remained high even after controlling for traditional cerebrovascular risk factors. Given that stroke and its consequences are associated with a high risk of death,¹⁸ these results suggest that cerebrovascular events are among the factors contributing to the high death rates in patients with BP.

In this study, a greater proportion of strokes among patients with BP relative to control subjects was ischemic in nature (72% versus 61%, $P < 0.001$, not shown in tables). This finding is consistent with previous reports showing that patients with BP are at greater risk of arterial or venous thrombosis. Using a retrospective cohort study, Roujeau et al demonstrated that the number of deaths from cardiovascular diseases in patients diagnosed with BP was higher than expected in the general population of the same age and sex.¹² In a case series, Echigo et al reported that thromboembolism occurred in 7 of 20 (35%) patients with autoimmune blistering disease, including BP. The type of organs involved varied and included the brain and lung.¹⁹ A recent population-based study found that patients with BP are 3 times as likely to develop pulmonary embolism.²⁰

To the best of our knowledge, this is the first population-based study to investigate the risk of stroke in a national cohort of patients with BP. The annual incidence of BP calculated from our database was 3.4 per 100 000 population, which is consistent with the previously reported incidence rate, ranging from 0.7 to 4.3 per 100 000 per year.^{1,21–23} According to the literature, patients diagnosed with BP are more likely to have a history of cerebral stroke, ranging from 7.7% to 19.1%.^{12,24–26} To avoid any confusion caused by pre-existing cerebrovascular disease, patients with a history of any type of stroke before the onset of BP were excluded from this study. By including only first-time cerebrovascular events that occurred after the diagnosis of BP, this 3-year follow-up study addresses the temporal relationship between BP and stroke. Results show that patients with BP are prone to develop ischemic stroke independent of other major risk factors of cerebrovascular event, including hypertension, diabetes mellitus, hyperlipidemia, and cardiovascular disease.

Recent research suggests that BP is an autoimmune sub-epidermal blistering disease with systemic inflammation involving more than just the skin. Both T helper 1 and T helper 2 immune response play an important role in the pathogenesis of BP.^{27,28} Multiple proinflammatory cytokines, including interleukin (IL)-1, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, tumor necrosis factor- α , and interferon- γ , increased in the sera of patients with BP.^{13,29–33} The serum levels of cytokines such as tumor necrosis factor- α and IL-6 are positively correlated to the disease activity, as indicated by the number of skin lesions.¹³ Moreover, elevated serum levels of soluble E-selectin and vascular endothelial growth factor in BP further support the activation of endothelial inflammatory and immune reactions.^{14,34} There is increasing evidence that the

pathogenesis and progression of atherosclerosis, plaque rupture, thrombosis, and stroke involve inflammatory processes and endothelial dysfunction.^{16,35,36}

Another possible explanation for the high risk of stroke in patients with BP is the hypercoagulation state related to antiphospholipid antibodies (aPLs). aPLs are a heterogeneous group of antibodies, including lupus anticoagulant, anticardiolipin antibody, and anti- β 2 glycoprotein I antibody.³⁷ These antibodies frequently appear in systemic lupus erythematosus³⁸ but have also been detected in organ-specific autoimmune diseases such as insulin-dependent diabetes mellitus,³⁹ myasthenia gravis,⁴⁰ autoimmune thyroid diseases,⁴¹ and inflammatory bowel disease.⁴² A recent study shows that aPLs were detected in 10 of 20 patients with autoimmune blistering disease, including 2 of 4 patients with BP. Among 10 patients who tested positive for aPLs, 7 patients had thromboembolisms, although most of them were clinically asymptomatic.¹⁹ aPLs can produce a prothrombotic state through inhibition of natural anticoagulant pathways, inhibition of fibrinolytic mechanisms, and induction of endothelial cell procoagulant activity. These processes predispose the patient to thrombotic events, particularly ischemic stroke.^{43,44} Because the current study lacks laboratory findings regarding aPLs, further research is needed to explore the relationship between aPLs and the risk of stroke in patients with BP.

Most patients with BP acquire the disease in old age, when they tend to have atherosclerosis. The chronic inflammation and hypercoagulable state associated with BP can exacerbate pre-existing atheroma and promote thrombus formation.³⁶ Note that patients with BP with acute stroke are more likely to experience poststroke respiratory and urinary tract infections and subsequent poor outcomes or even death because of their older age and glucocorticoid-related immunosuppression.^{45,46} Therefore, physicians should not overlook the increased risk of stroke after the onset of BP.

Our study has some limitations. First, patients with BP were identified by diagnostic code in a database. There remains the possibility of misclassification of BP because of coding errors or misdiagnosis; this nondifferential misclassification might bias the results toward the null hypothesis. Second, residual confounding cannot be excluded. For example, the NHI database used in this study does not contain data on some variables that may also influence the risk of stroke such as obesity, smoking behavior, alcohol consumption, and dietary habit. Additionally, the medical comorbidities (eg, hypertension, atrial fibrillation, diabetes) adjusted for in the multivariate analysis were identified by diagnostic codes. Therefore, the analysis adjusted for the presence or absence of the condition and not the severity of the comorbidity. Residual confounding may exist due to unmeasured differences in severity between patients with BP and control subjects, more so if the comorbidities also affect the risk of stroke. Third, patients with BP may be more likely to be diagnosed with minor stroke due to an increased frequency of CT/MRI scans among these patients. However, it is unlikely that patients with acute stroke in Taiwan with any stroke symptom would be either denied or fail to get admitted to an emergency department within 24 hours. This is because of widespread access to emergency medical services and very

low out-of-pocket payment after the establishment of a nationwide Emergency Medical Services System and the National Health Insurance system, respectively. Furthermore, after excluding transient ischemic attack (regarded as minor stroke), the relationship between BP and subsequent stroke is sustained; compared with patients without BP, the adjusted HR for stroke among patients with BP is 2.29 (95% CI, 1.69 to 3.25; $P < 0.001$), over twice the likelihood observed in comparison patients in the 3-year follow-up period. Finally, data about the clinical severity of BP such as the percentage of body surface affected or number of blisters/erosions were not available. This prevented our study from assessing the dose-response relationship between BP severity and risk of stroke.

In conclusion, this large population-based study finds that patients with BP have an increased risk of stroke and particularly ischemic stroke. Future studies that include clinical markers of BP severity, serum level of proinflammatory cytokines, and serological studies of aPLs can clarify the underlying pathomechanisms between BP and stroke.

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Disclosures

None.

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