Increased Risk of Stroke After a Herpes Zoster Attack
A Population-Based Follow-Up Study

Jiunn-Horng Kang, MSc, MD; Jau-Der Ho, PhD, MD; Yi-Hua Chen, PhD; Herng-Ching Lin, PhD

Background and Purpose—Varicella zoster virus-induced vasculopathy and postherpes zoster attack stroke syndromes have been reported previously; nevertheless, data regarding the exact prevalence and risk of stroke occurring postherpes zoster attack are still lacking. This study aims to investigate the frequency and risk of stroke after a herpes zoster attack using a nationwide, population-based study of a retrospective cohort design.

Method—A total of 7760 patients who had received treatment for herpes zoster between 1997 and 2001 were included and matched with 23 280 randomly selected subjects. A 1-year stroke-free survival rate was then estimated using the Kaplan-Meier method. After adjusting for potential confounders, Cox proportional hazard regressions were carried out to compute the adjusted 1-year survival rate.

Results—Of the sampled patients, 439 patients (1.41%) developed strokes within the 1-year follow-up period, that is, 133 individuals (1.71% of the patients with herpes zoster) from the study cohort and 306 individuals (1.31% of patients in the comparison cohort) from the comparison cohort. The log rank test indicated that patients with herpes zoster had significantly lower 1-year stroke-free survival rates than the control ($P<0.001$). The adjusted hazard ratios of stroke after herpes zoster and herpes zoster ophthalmicus during the 1-year follow-up period were 1.31 and 4.28, respectively.

Conclusion—The risk for stroke increased after a zoster attack. Although varicella zoster virus vasculopathy is a well-documented complication that may induce a stroke postherpes zoster attack, it does not fully account for the unexpectedly high risk of stroke in these patients. **(*Stroke*. 2009;40:3443-3448.)**

Key Words: herpes zoster ■ herpes zoster attack ■ stroke

The primary varicella zoster virus (VZV) infection usually affects children, leading to varicella (chicken pox). Although some infected children may develop serious complications, varicella is generally benign and transient.[1] The VZV then becomes inactive in the sensory and autonomic ganglia. Although the pathomechanisms are not fully understood, spontaneous reactivation of VZV manifests as skin lesions with painful vesicles spreading over one to 1 dermatomes known as a herpes zoster (shingle). Herpes zoster is an observed condition in elderly, immunocompromised, and debilitated patients.[2] It usually resolves itself spontaneously, although the development of long-duration postherpetic neuralgia is not uncommon.[3]

Numerous reports of VZV-induced vasculopathy and stroke syndrome after herpes zoster attacks have been reported since the early 1970s.[4,5] VZV is also the only recognized human virus able to replicate in cerebral arteries.[6] It is hypothesized to spread along the nerve fibers to the blood vessels where it induces further inflammatory and thrombotic responses.[2,7,8] Two major spectrums of VZV vasculopathy have been identified: large- and small-vessel VZV vasculopathy.[9] In large-vessel VZV vasculopathy, the involved vessels are damaged by virus-induced inflammation,[2] presented as granulomatous angiitis in pathology, and can result in stroke.[5,10] Small-vessel VZV vasculopathy has many nonspecific manifestations such as fever, headache, seizures, weakness, consciousness disturbances, and cognitive impairments, known as small-vessel encephalitis.[10]

To our knowledge, despite many case reports of conditions associated with VZV vasculopathy, large sample data regarding the exact frequency and risk of stroke occurring postherpes zoster attack are still lacking. Our study's goal was to investigate the risk and frequency of stroke after herpes zoster attacks in the general population using a nationwide population-based study of a retrospective cohort design.

Methods

Database

This study used a data set released by the Taiwan National Health Research Institute in 2006. Taiwan began its National Health Insurance program in 1995 to finance health care for all the island's residents. There are currently >25 million enrollees covered by the

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program, representing approximately 98% of the island's population. This data set, which the Taiwan National Health Research Institute created by systematically selecting a representative database from the entire set of enrollees, consists of 1 000 000 randomly selected subjects. There were no statistically significant differences in age, sex, or healthcare costs between the sample group and all enrollees, as reported by the Taiwan National Health Research Institute. This data set includes all claims data for these 1 000 000 subjects, offering a unique opportunity to explore the risk of stroke among patients with herpes zoster.

Because the data set used in this study consists of deidentified secondary data released to the public for research purposes, this study was exempt from full review by the Institutional Review Board.

Study Sample

This study includes a study cohort and a comparison cohort. The study cohort comprised all patients who had visited ambulatory care centers for treatment of herpes zoster (*International Classification of Diseases, 9th Revision, Clinical Modification* Code 053) over a 5-year period, from January 1, 1997, to December 31, 2001 (n=9841). We excluded patients <18 years of age (n=1437) to limit the study sample to adults. We also excluded patients who had been diagnosed with a stroke (*International Classification of Diseases, 9th Revision, Clinical Modification* Codes 430 to 438) before their index ambulatory care visit (first-time ambulatory care visits for treatment of herpes zoster). Ultimately, our study cohort included 7760 patients with herpes zoster.

Meanwhile, the comparison cohort was selected from the remaining patients in the data set. We excluded patients who had been diagnosed with herpes zoster or stroke before 2001. We then randomly extracted 23 280 subjects (3 for every patient in the study cohort) matching the study cohort in terms of age (as a continuous variable) and sex. We also selected their first ambulatory care visit during 2001 as their index ambulatory care visit. Thereafter, each patient was tracked for 1 year from their index ambulatory to distinguish patients who had developed any type of stroke.

Statistical Analysis

The SAS statistical package (SAS System for Windows, Version 8.2) was used to perform analyses in this study. Pearson χ^2 tests were performed to examine the differences between the 2 cohorts in terms of sociodemographic characteristics, select comorbid medical disorders, and stroke development risk. The 1-year stroke-free survival rate was estimated by the Kaplan-Meier method using the log rank test to examine the differences in the risk of developing stroke between the 2 cohorts.

In addition, after adjusting for potential confounders, Cox proportional hazard regressions were carried out to compute the 1-year survival rate. Potential confounders included patient's age, sex, monthly income, level of urbanization (including 5 levels, with Level 1 referring to "most urbanized" and Level 5 referring to "least urbanized" communities), geographical location of the community in which the patient resided (northern, central, eastern, and southern Taiwan), and whether a patient had hypertension, diabetes, renal disease, coronary heart disease, hyperlipidemia, atrial fibrillation, heart failure, heart valve/myocardium disease, and/or carotid/peripheral vascular disease. Previous studies have reported that the occurrence of stroke is associated with both geographical region and level of urbanization[11,12]; these have therefore been adjusted in the regression modeling. The reason we selected NT $15 840 as the first income-level cutoff point was that this is the government-stipulated minimum wage for full-time employees in Taiwan. Finally, we present hazard ratios (HRs) along with 95% CIs using a significance level of 0.05.

Table 1. Demographic Characteristics and Comorbid Medical Disorders for Patients in Taiwan With Herpes Zoster and Patients in the Comparison Cohort, 1999 to 2001 (n=31 040)

	Patients With Herpes Zoster		Comparison Patients		
Variable	Total No.	Column Percent	Total No.	Column Percent	*P* Value
Hypertension					<0.001
Yes	416	5.36	993	4.27	
No	7344	94.64	22 287	95.73	
Diabetes					0.001
Yes	221	2.85	508	2.18	
No	7539	97.15	22 772	97.82	
Coronary heart disease					<0.001
Yes	151	1.95	303	1.30	
No	7609	98.05	22 977	98.70	
Hyperlipidemia					0.131
Yes	86	1.11	213	0.91	
No	7674	98.89	23 067	99.09	
Renal disease					0.014
Yes	28	0.36	47	0.20	
No	7732	99.64	23 233	99.80	
Atrial fibrillation					0.700
Yes	10	0.13	26	0.11	
No	7750	99.87	23 254	99.87	
Heart failure					0.006
Yes	42	0.54	75	0.32	
No	7718	99.46	23 205	99.68	
Heart valve/myocardium disease					0.518
Yes	27	0.35	70	0.30	
No	7733	99.65	23 210	99.70	
Carotid/peripheral vascular disease					0.028
Yes	16	0.21	24	0.10	
No	7744	99.79	23 256	99.90	
Monthly income					0.044
0	4098	52.81	12 324	52.94	
NT $1-15 840	759	9.78	2308	9.91	
NT $15 841-25 000	1939	24.99	6017	25.85	
≥NT $25 001	964	12.42	2631	11.30	
Urbanization level					0.794
1	1402	18.07	4240	18.21	
2	1323	17.05	4025	17.29	
3	711	9.16	2218	9.53	
4	671	8.65	1983	8.52	
5	3653	47.07	10 814	46.45	
Geographic region					0.001
Northern	5351	68.96	15 886	68.24	
Central	1130	14.56	3241	13.92	
Southern	1150	14.82	3837	16.48	
Eastern	129	1.66	316	1.36	

Results

The mean age for the sampled patients was 46.7 years with a SD of 15.6 years. Table 1 presents the distribution of demographic characteristics and selects comorbid medical disorders for both the study and comparison cohorts. After matching for sex and age, the results demonstrate that patients with herpes zoster were more likely to have comorbidities such as hypertension ($P<0.001$), diabetes ($P=0.001$), coro-

Table 2. Crude and Adjusted HRs for Stroke Among Sample Patients During the 1-Year Follow-Up Period Starting From the Index Ambulatory Care Visit (n=31 040)

	Total Sample		Comparison		Herpes Zoster, Total		Herpes Zoster Ophthalmicus	
Presence of Stroke	No.	Percent	No.	Percent	No.	Percent	No.	Percent
One-year follow-up period								
Yes	439	1.41	306	1.31	133	1.71	7	5.83
No	30 601	98.59	22 974	98.69	7627	98.29	113	94.17
Crude HR (95% CI)	—		1.00		1.31† (1.07–1.61)		4.59‡ (2.12–9.93)	
Adjusted* HR (95% CI)	—		1.00		1.31† (1.06–1.60)		4.28‡ (2.01–9.03)	

*Adjustments are made for patient's age, sex, hypertension, diabetes, coronary heart disease, hyperlipidemia, renal disease, atrial fibrillation, heart failure, heart valve/myocardium disease, carotid/peripheral vascular disease, monthly income, urbanization level, and geographical region.

†$P<0.05$.

‡$P<0.001$.

nary heart disease ($P<0.001$), renal disease ($P=0.014$), heart failure ($P=0.006$), and carotid/peripheral vascular disease ($P=0.028$) at the time of their outpatient care visits as compared with the patients in the comparison cohort.

Of the total sample of 31 040 patients, 439 individuals (1.41%) developed strokes during the 1-year follow-up period, 133 (1.71%) of which were patients with herpes zoster and 306 (1.31%) that were patients in the comparison cohort (Table 2). The log rank test indicated that patients with herpes zoster had significantly lower 1-year stroke-free survival rates than patients in the comparison cohort ($P<0.001$). The results of Kaplan-Meier survival analysis are presented in the Figure.

Details of the crude and adjusted HRs for stroke, based on Cox proportional hazard regression analysis, are also presented in Table 2 by cohort. After adjusting for patient's age, sex, monthly income, hypertension, diabetes, renal disease, coronary heart disease, hyperlipidemia, atrial fibrillation, heart failure, heart valve/myocardium disease, carotid/peripheral vascular disease, level of urbanization, and the geographical location of the community in which the patient resided, the HR for developing stroke during the 1-year follow-up period was 1.31 (95% CI, 1.00 to 1.60; $P<0.05$) for patients with herpes zoster compared with patients in the comparison cohort. We further analyzed the risk of stroke for patients with herpes zoster ophthalmicus. We found that the adjusted HR of stroke during the 1-year follow-up period was 4.28 (95% CI, 2.01 to 9.03; $P<0.001$) for patients with herpes zoster and ophthalmic complications as compared with patients without herpes zoster.

We also analyzed the risk of stroke by stroke type, finding that the adjusted HR of developing ischemic stroke and intracerebral or subarachnoid hemorrhaging during the 1-year follow-up period was 1.31 (95% CI, 1.07 to 1.65; $P=0.009$) and 2.79 (95% CI, 1.69 to 4.61; $P<0.001$), respectively, for patients with herpes zoster compared with patients of the comparison cohort.

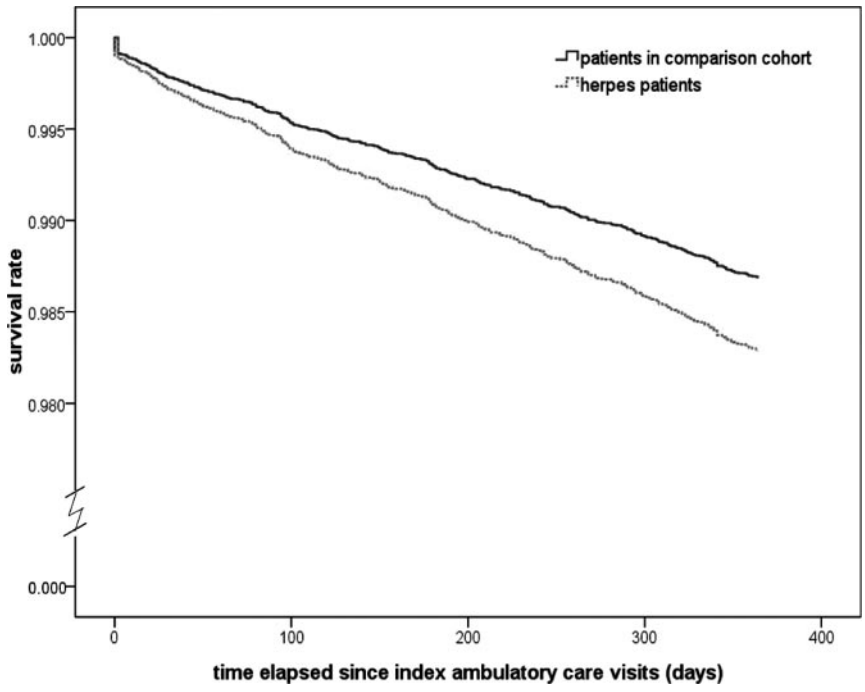

Figure. Stroke-free survival rates for patients with herpes zoster in Taiwan and patients in the comparison cohort, 1999 to 2001.

Table 3. Crude and Adjusted HRs for Stroke Among Sample Patients During the 1-Year Follow-Up Period Stratified by Patient Age and Sex (n=31 040)

	Patient Sex*				Patient Age,† Years			
	Male		Female		<45		≥45	
Presence of Stroke	Comparison No. (%)	Herpes Zoster No. (%)	Comparison No. (%)	Herpes Zoster No. (%)	Comparison No. (%)	Herpes Zoster No. (%)	Comparison No. (%)	Herpes Zoster No. (%)
One-year follow-up period								
Yes	161 (1.4)	72 (1.9)	149 (1.2)	65 (1.6)	28 (0.3)	10 (0.3)	282 (2.2)	127 (2.9)
No	11 047 (98.6)	3664 (98.1)	11 923 (98.9)	3959 (98.4)	10 190 (99.7)	3396 (99.7)	12 780 (97.8)	4227 (97.1)
Crude HR (95% CI)	1.00	1.35‡ (1.02–1.79)	1.00	1.32‡ (1.01–1.76)	1.00	1.07 (0.52–2.21)	1.00	1.36§ (1.10–1.68)
Adjusted HR (95% CI)	1.00	1.32‡ (1.01–1.75)	1.00	1.30‡ (1.01–1.75)	1.00	1.02 (0.49–2.12)	1.00	1.31‡ (1.06–1.63)

*The HR was calculated by adjusting for patient's age, hypertension, diabetes, coronary heart disease, hyperlipidemia, renal disease, atrial fibrillation, heart failure, heart valve/myocardium disease, carotid/peripheral vascular disease, monthly income, urbanization level, and geographical region.

†The HR was calculated by adjusting for patient's sex, hypertension, diabetes, coronary heart disease, hyperlipidemia, renal disease, atrial fibrillation, heart failure, heart valve/myocardium disease, carotid/peripheral vascular disease, monthly income, urbanization level, and geographical region.

‡$P<0.05$.

§$P<0.001$.

Table 3 reveals results from further analyses stratified by patient age and sex. Among male and female patients, the adjusted HR of stroke during the 1-year follow-up period was, respectively, 1.32 (95% CI, 1.01 to 1.75; $P<0.05$) and 1.30 (95% CI, 1.01 to 1.75; $P<0.05$) times greater for those with herpes zoster than for those without. In addition, the adjusted HR for stroke occurring during the 1-year follow-up period was 1.31 (95% CI, 1.06 to 1.63; $P<0.05$) times higher for patients with herpes zoster ≥45 years old than for the same age group of the comparison cohort. However, there were no significant differences in stroke risk between patients with herpes zoster <45 years old and patients in the same age group of the comparison cohort.

Discussion

Varicella is considered an important risk factor for stroke in children.[13] Askalan et al showed that compared with the general population, there is a 3-fold increase in acute ischemic stroke among children with preceding varicella infection.[13] However, data regarding stroke frequency after zoster attacks in adults are lacking. VZV vasculopathy resulting in stroke is considered a rare complication of postherpes zoster attacks in adults; nevertheless, our data suggest that stroke patterns after instances of herpes zoster may not only be sporadic cases. According to the 1-year follow-up data, the frequencies of stroke after herpes zoster and herpes zoster ophthalmicus attacks were 1.71% and 5.83%, respectively. After adjusting for other cerebrovascular risks, we found that the risk of having a stroke increased by 31% postherpes zoster attacks, and approximately 4-fold in the patients with herpes zoster ophthalmicus, compared with the comparison cohort. Because previous studies demonstrate that herpes zoster (shingles) frequency could be as high as 1.3 to 1.6 per 1000 people per year, and the OR for lifetime occurrences is approximately one to 4,[14,15] the possibility of developing a stroke after a herpes zoster attack should not be overlooked.

Furthermore, we found that the elevated HR for stroke development after herpes zoster was significant among patients who were ≥45 years old. We hypothesize that the frequency and severity of vasculopathy after herpes zoster may increase in elderly individuals prone to pre-existing arthrosclerosis and attenuated immunological statuses. Interestingly, although the risks for hemorrhagic and ischemic stroke both increased in patients with herpes zoster, the HR for the former was higher. Previous articles have illustrated that VZV vasculopathy can result in a variable spectrum of clinical manifestations, including arterial thrombosis,[4] arterial dolichoectasia,[16] dissection,[17] aneurysm,[18] and hemorrhaging.[19,20] The frequency of stroke subtypes varies by ethnicity.[21] For instance, scientific literature indicates a higher prevalence of hemorrhagic stroke in Asian/Chinese populations.[21,22] It is still unknown whether stroke subtypes postherpes zoster attack are influenced by such ethnic distinctions. We suggest further exploration into this matter.

Although VZV vasculopathy is a well-documented cause of stroke after herpes zoster attacks, it does not fully explain the unexpectedly high risk of stroke observed among these patients. In addition to direct causation by VZV vasculopathy, we hypothesize several possible pathological stroke mechanisms. First, although current data are limited, it is possible that for patients with mild VZV vasculopathy, the damaged vessel initiates secondary atherosclerosis in the long run. The gradual progression of atherosclerosis may cause delayed stroke in these patients. Second, patients often experience postherpetic neuralgia after a herpes zoster attack.[23] Chronic pain may be associated with elevated sympathetic statuses and adverse emotional reactions,[23,24] theoretically increasing cerebrovascular risks. Third, it is generally accepted that persons who experience stressful events and medical conditions may be associated with the herpes zoster reactivation and attack. Despite adjusting for several well-known cardio-

vascular risk factors, the immunologic status and general health condition of the subjects could not be inferred from the administrative data. Therefore, the possibility that stroke development is associated with underlying debilitating or stressful conditions cannot be excluded. Further study is recommended to verify our hypotheses.

A majority of previous reports show that contralateral hemiplegia is the most common manifestation of VZV vasculopathy resulting in stroke, particularly after herpes zoster ophthalmicus.[4,25] Our findings are consistent with this observation.

It is worthy to mention that some authors reported a relationship between VZV vasculopathy and stroke developing when shingles involved distant dermatomes such as cervical, thoracic, and even sacral regions.[7,26,27] Similarly, we found that the overall risk for having a stroke increased in patients with herpes zoster. The pathomechanisms explaining this phenomenon are still unknown; however, there is some speculation that it involves the dissemination or co-occurrence of viral reactivation in cerebral ganglia spreading to the supplying vessels.[7] Systemic factors may also contribute to stroke. Recently, coagulation abnormalities have been reported in association with herpes zoster attacks.[28] The clinical implications of these findings could be important for stroke prevention and patient management.

Finally, we found a higher frequency of several cardiovascular risk factors among the patients with herpes zoster compared with the case-matching group. To our knowledge, the data regarding cardiovascular risk frequency among patients with herpes zoster are still lacking. The "herpesvirus burden" could accelerate arthrosclerosis development, which could be associated with some cardiovascular factors.[29,30] In addition, the patient who has cardiovascular factors might also have poorer health, putting them at risk of herpes zoster. We postulate that this cause-and-effect relationship between shingles and cardiovascular risk factors is bidirectional. Nevertheless, stroke development risk remained higher in patients with herpes zoster after adjusting for these cardiovascular risk factors.

Our study has some limitations. Skin lesions are a common diagnosis indicator for herpes zoster and, when absent, may make accurate clinical diagnoses more difficult.[31] Hence, patients may have been absent or and miscoded in our database. Furthermore, the clinical features and manifestations of herpes zoster vasculopathy may be different among comorbid patients. For example, the VZV small-vessel vasculopathy in a patient with HIV could manifest as encephalitis rather than a stroke,[10] which was not included in our study. Finally, potential confounding variables, including obesity, physical activity, smoking and alcohol use, dietary habits, and family history, are associated with stroke but not indicated in our database. The association between herpes zoster and theses factors remains unknown. Further study is suggested to clarify these issues.

Conclusion

To our knowledge, this is the first attempt at investigating epidemiological data on strokes after zoster attacks in a large nationwide population-based study. We confirmed that in the general population, the risk for stroke increased after a zoster attack and additionally found that strokes after such attacks were more frequent than expected. Further studies should be conducted to explore the underlying pathomechanisms and intervention strategies for patients experiencing herpes zoster attacks.

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Disclosure

None.

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