

Increased Risk of Anterior Uveitis Following Herpes Zoster

A Nationwide Population-Based Study

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Objective: To investigate the relationship between herpes zoster (HZ) and the subsequent risk of anterior uveitis during the year following an HZ diagnosis, using a nationwide population-based data set.

Methods: This study used the Taiwan National Health Insurance Research Database. The study cohort consisted of 314 405 patients who received a diagnosis of HZ. The comparison cohort comprised 943 215 randomly selected patients. We tracked each patient for a 1-year period from their index ambulatory care visit to identify those who subsequently received a diagnosis of anterior uveitis. Stratified Cox proportional hazard regressions were performed to compute the adjusted 1-year uveitis-free survival rate, after adjusting for patient's age, sex, and geographic region and the presence of rheumatoid arthritis, psoriasis, mumps, systemic lupus erythematosus, tuberculosis, ankylosing spondylitis, and human immunodeficiency syndrome/AIDS.

Results: During the 1-year follow-up period, 2515 (0.2%) of 1 257 620 sampled patients were diagnosed with anterior uveitis: 908 from the study cohort (0.3% of the patients with HZ) and 1607 from the comparison cohort (0.2% of patients without HZ). After adjusting for potential confounders, the hazard ratio of anterior uveitis during the 1-year follow-up period was 1.67 for patients with HZ ($P < .001$) compared with the comparison cohort. In addition, the hazard ratio of anterior uveitis for patients with HZ ophthalmicus was 13.06 ($P < .001$) when compared with patients without HZ.

Conclusions: The risk of anterior uveitis increased in the year following a diagnosis of HZ. We suggest that patient eye condition be evaluated following diagnosis with HZ.

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HERPES ZOSTER (HZ) INFECTION arises when varicella-zoster virus (VZV) reactivates later in life. After the primary infection, VZV remains latent in dorsal root ganglia, cranial nerve ganglia, and autonomic ganglia. Herpes zoster characteristically leads to a painful vesicular rash with unilateral dermatomal distribution. Infection with HZ usually resolves within 2 to 4 weeks.¹ This affects 1 in 4 people in a lifetime, and the risk increases markedly after the age of 50 years because of an age-related decrease in VZV-specific cell-mediated immunity.^{2,3} In population-based studies, the incidence of HZ rises with age, from approximately 2 to 3 cases per 1000 patient-years in people aged 50 to 8 cases per 1000 patient-years in those 70 and older.⁴ In addition, HZ has been associated with suppressed immune status and may be fatal in immunosuppressed or critically ill patients.⁵

Uveitis is a general term used to describe inflammation of the uveal tract due to any cause. It usually includes a num-

ber of diverse diseases affecting not only the uvea but also the retina and vitreous. The etiology is difficult to establish because the exact cause of uveitis frequently remains unknown.^{6,7} Various generalized diseases have been associated with uveitis.⁸ To our knowledge, there have been few large population-based studies on the relationship between HZ and uveitis. Using a nationwide population-based data set from Taiwan, this study investigated the relationship between HZ and the subsequent risk of anterior uveitis development in the 1-year period following HZ diagnosis.

METHODS

DATABASE

Taiwan launched its single-payer National Health Insurance (NHI) program in March 1995 to finance health care for all citizens of Taiwan. As of 2008, Taiwan's NHI program covered 22.89 million of the country's 22.96 million people (amounting to 99.7% of the is-

Table 1. Baseline Data for 1 257 620 Sampled Patients in Taiwan, 2003-2005

Variable	No. (% of Patients)		P Value
	With HZ (n = 314 405)	Without HZ (n = 943 215)	
Sex			
Male	164 545 (52.3)	493 635 (52.3)]. >.99
Female	149 860 (47.7)	449 580 (47.7)	
Age, mean (SD), y	51.7 (17.8)	51.5 (17.7)	.43
Age, y			
18-44	108 077 (34.4)	324 231 (34.4)]. >.99
45-64	121 948 (38.8)	365 844 (38.8)	
>64	84 380 (26.8)	253 140 (26.8)	
Year of index visit			
2003	100 338 (31.9)	301 014 (31.9)]. >.99
2004	105 547 (33.6)	316 641 (33.6)	
2005	108 520 (34.5)	325 560 (34.5)	
Rheumatoid arthritis	4494 (1.4)	10 018 (1.1)	<.001
Psoriasis	2486 (0.8)	6034 (0.6)	<.001
Mumps	164 (0.1)	252 (0.1)	<.001
Tuberculosis	2802 (0.9)	5888 (0.6)	<.001
Systemic lupus erythematosus	1105 (0.4)	1083 (0.1)	<.001
HIV/AIDS	444 (0.1)	572 (0.1)	<.001
Ankylosing spondylitis	1252 (0.4)	1227 (0.1)	<.001
Geographic region of Taiwan			
Northern	156 199 (49.7)	441 841 (46.8)]. <.001
Central	59 035 (18.8)	169 266 (18.0)	
Southern	91 392 (29.1)	287 849 (30.5)	
Eastern	7779 (2.5)	44 259 (4.7)	

Abbreviations: HIV, human immunodeficiency virus; HZ, herpes zoster.

land's population). This study used the NHI Research Database (NHIRD), derived from Taiwan's NHI program and provided to scientists in Taiwan for research purposes. The NHIRD provides a registry of medical facilities and board-certified physicians, as well as monthly claim summaries for inpatient and ambulatory care claims, details of inpatient and ambulatory care orders, and expenditures for prescriptions dispensed at contracted pharmacies. The longitudinal nature of the NHIRD allowed the researchers to trace all medical services use for enrollees from 1996 to 2008. Therefore, this database also provides a valuable resource for examining the risk of developing uveitis among patients diagnosed with HZ.

Because the NHIRD consists of deidentified secondary data released to the public for research purposes, the study was waived from review by the Taipei Medical University Institutional Review Board.

STUDY SAMPLE

This study was designed as a retrospective case-cohort study. All patients who visited outpatient departments of hospitals or clinics for the treatment of HZ (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 053) from January 1, 2003, to December 31, 2005, were extracted from the NHIRD (N=349 477). We assigned their first ambulatory care visits for treatment of HZ as the index ambulatory care visit. To limit our study sample to the adult population, we first excluded patients who were younger than 18 (n=32 701). To increase the likelihood of selecting only new cases, we then excluded patients who had been diagnosed with HZ before the year 2003 (n=1028). Furthermore, we excluded patients who had received a diagnosis of anterior uve-

itis (ICD-9-CM codes 364 or 364.0-364.4) before their index ambulatory care visits (n=1343). The resulting 314 405 patients with HZ were included in the study cohort.

We likewise selected the comparison cohort for this study from the 2003 to 2005 Registry of Beneficiaries of the NHIRD. First we excluded patients who had received a diagnosis of HZ between 1996 and 2006. We then used the SAS Proc Surveyselect program (SAS, version 8.2; SAS Institute Inc) to randomly extract 943 215 beneficiaries (3 for every patient with HZ), matched with the study cohort in terms of age, sex, and the index year of ambulatory care visit. We assigned their first ambulatory care visits occurring in the index year as their index ambulatory care visits. We also ensured that the selected patients did not include patients who had anterior uveitis before their index ambulatory care visits. Then we tracked each patient for 1 year from his or her index visit to identify patients who subsequently had anterior uveitis.

STATISTICAL ANALYSIS

This study used the SAS statistical package, version 8.2, to perform all statistical analyses. We used *t* tests and Pearson χ^2 tests to examine the differences in terms of sociodemographic characteristics and comorbidities between these 2 cohorts. The selected comorbidities included rheumatoid arthritis (RA), psoriasis, mumps, systemic lupus erythematosus (SLE), tuberculosis, ankylosing spondylitis (AS), and human immunodeficiency syndrome (HIV)/AIDS, which previous reports had associated with anterior uveitis. These comorbid conditions were counted only if the condition occurred either in the inpatient setting or in 2 or more ambulatory care claims coded 1 year before and after the index ambulatory care visit. In addition, the log-rank test was conducted to estimate the difference in the risk of anterior uveitis between patients with and without HZ. Finally, stratified Cox proportional hazard regressions (stratified by age, sex, and the year of index ambulatory care visit) were performed to calculate the 1-year uveitis-free survival rate, after adjusting for the geographic location of the patient's residence (Northern, Central, Eastern, and Southern Taiwan) and selected comorbidities. Significance was set at 2-tailed $P \leq .05$ in this study.

RESULTS

The distribution of demographic characteristics and comorbidities for patients with and without HZ is presented in **Table 1**. Of the total 1 257 620 sampled patients, the mean (SD) age was 51.6 (17.8) years. After matching for sex, age, and the year of index ambulatory care visit, patients with HZ were more likely to have RA, psoriasis, mumps, SLE, tuberculosis, AS, and HIV/AIDS than were patients without HZ (all $P < .001$). In addition, patients with HZ were more likely to reside in the northern part of Taiwan compared with patients without HZ ($P < .001$). Patients without HZ had a greater tendency to live in the eastern part of Taiwan compared with patients with HZ ($P < .001$).

Table 2 shows the incidence of anterior uveitis among patients with and without HZ. A total of 2515 (0.2%) of 1 257 620 patients were diagnosed with anterior uveitis during the 1-year follow-up period: 908 from the study cohort (0.3% of the patients with HZ) and 1607 from the comparison cohort (0.2% of patients without HZ). The log-rank test reveals that patients with HZ had significantly lower 1-year uveitis-free survival rates compared with patients in the comparison cohort ($P < .001$).

Table 2. Crude HR for Uveitis Among Sampled Patients During the 1-Year Follow-up^a

Variable	Value		
	All Patients (N = 1 257 620)	Patients With HZ (n = 314 405)	Patients Without HZ (n = 943 215)
Total uveitis, No. (%)			
Yes	2515 (0.2)	908 (0.3)	1607 (0.2)
No	1 255 105 (99.8)	313 497 (99.7)	941 608 (99.8)
Crude HR (95% CI)	...	1.70 (1.56-1.84) ^b	1 [Reference]

Abbreviations: HR, hazard ratio; HZ, herpes zoster.

^aStarting from the index ambulatory care visit.

^b $P < .001$.

Table 3. Covariate-Adjusted HRs for Uveitis Among 1 257 620 Sampled Patients During the 1-Year Follow-up^a

Variable	HR (95% CI)	P Value
Group		
Herpes zoster	1.67 (1.54-1.81)	<.001
Comparison	1 [Reference]	
Geographic region		
Northern	1 [Reference]	...
Central	1.04 (0.93-1.15)	.53
Southern	0.96 (0.87-1.05)	.36
Eastern	1.08 (0.89-1.31)	.42
Rheumatoid arthritis	1.34 (1.01-1.81)	.04
Psoriasis	1.27 (1.02-1.55)	.03
Tuberculosis	1.06 (0.71-1.57)	.78
Systemic lupus erythematosus	2.61 (1.44-4.72)	.002
Mumps	1.11 (0.16-7.93)	.92
Ankylosing spondylitis	2.69 (1.18-6.14)	.02
HIV/AIDS	3.25 (0.63-16.85)	.82

Abbreviations: HIV, human immunodeficiency virus; HR, hazard ratio.

^aUsing Cox proportional regression stratified by patient's age, sex, and the year of index ambulatory care visit. The year started from the index ambulatory care visit.

Table 2 also presents crude hazard ratios (HRs) for anterior uveitis between the study and comparison cohorts. Stratified Cox proportional hazard regressions (stratified by age, sex, and the year and month of the index visit) shows the HR of anterior uveitis during the 1-year follow-up period for patients with HZ was 1.70 (95% CI, 1.56-1.84; $P < .001$) compared with patients without HZ.

Table 3 also shows the covariate-adjusted HR for anterior uveitis for patients with and without HZ. The risk of anterior uveitis during the 1-year follow-up period was 1.67 times greater (95% CI, 1.54-1.81; $P < .001$) for patients with HZ than for the comparison cohort, after adjusting for RA, psoriasis, mumps, SLE, tuberculosis, AS, and HIV/AIDS and geographic region. As expected, RA (HR, 1.34; 95% CI, 1.01-1.81; $P = .04$), psoriasis (1.27; 1.02-1.55; $P = .03$), SLE (2.61; 1.44-4.72; $P = .002$), and AS (2.69; 1.18-6.14; $P = .02$) were significantly associated with anterior uveitis during the 1-year follow-up period, after adjusting for other factors.

Table 4. Crude and Adjusted HRs for Uveitis Among the Sampled Patients During the 1-Year Follow-up^a

Variable	Value		
	All Patients (n = 942 072)	Patients With HZ Ophthalmic (n = 476)	Patients Without HZ Ophthalmic (n = 943 215)
Total uveitis, No. (%)			
Yes	1619 (0.2)	12 (2.5)	1607 (0.2)
No	942 072 (99.8)	464 (97.5)	941 608 (99.8)
Crude HR (95% CI)	...	15.15 (8.53-26.93) ^b	1 [Reference]
Adjusted HR (95% CI) ^c	...	13.06 (7.34-23.25) ^b	1 [Reference]

Abbreviations: HR, hazard ratio; HZ, herpes zoster.

^aStarting from the index ambulatory care visit.

^b $P < .001$.

^cAdjustments were made for patient's geographic location, rheumatoid arthritis, psoriasis, systemic lupus erythematosus, ankylosing spondylitis, and tuberculosis.

We further analyzed the HR for uveitis between the patients with HZ ophthalmic and the comparison cohort (**Table 4**). We found that when compared with the comparison patients, the HR of uveitis for patients with HZ ophthalmic was 13.06 (95% CI, 7.34-23.25; $P < .001$) after adjusting for patient's geographical location, RA, psoriasis, SLE, AS, and tuberculosis. We did not take HIV/AIDS into consideration in the regression model because of the small case numbers in some cells.

COMMENT

Uveitis is uncommon in the very young (younger than 10 years) and the very old (older than 70 years), and it most commonly troubles adults aged 20 to 50. According to previous reports, 10% of people younger than 65 who are registered as legally blind are visually compromised because of uveitis and its complications.^{8,9} However, according to our knowledge, no large-scale population-based study has been conducted to explore the relationship between HZ and subsequent uveitis. In this study, we found that the relative risk of anterior uveitis during the 1-year follow-up period for patients with HZ and HZ ophthalmic was 1.67 and 13.06 times, respectively, greater than the comparison cohort after taking age, sex, geographic region, RA, psoriasis, mumps, SLE, tuberculosis, AS, and HIV/AIDS into consideration in the regression modeling.

Uveitis is either a primary ocular condition or related to various systemic disorders. The reported frequency of systemic diseases underlying uveitis varies from 18% to 43% in different areas.^{6,10-14} Rosenbaum¹² described 236 patients with uveitis who were referred for medical examination and found systemic disease in 40% of patients. Reiter syndrome (7.2%) had the highest frequency, followed by sarcoidosis (5.5%) and AS (5.5%). In a hospital population in Sierra Leone, West Africa, the most common cause of uveitis was toxoplasmosis, occurring in 40 of 93 patients (43%).¹¹ Rothova et al⁶ reported systemic disease in 865 patients with uveitis, and a definite association was de-

terminated for 220 patients (25%). Sarcoidosis (7%) and HLA-B27-associated seronegative spondyloarthropathies (6%) were the most frequently observed systemic diseases. Syphilis and tuberculosis were responsible for 0.6% and 1.4%, respectively. Furthermore, presumed or definite toxoplasmosis was encountered in 10% of cases. In another series from a uveitis clinic in Taiwan, patients with Bechet disease accounted for 18% of 240 Chinese patients with uveitis.¹³ Few studies have reported the relationship between HZ and the subsequent risk of uveitis.

The mechanisms underlying the association between HZ and subsequent uveitis may include the following pathways. First, the VZV affects various ocular tissues possibly via neural, hematologic, or extrinsic spread.¹⁵ In patients with herpetic keratouveitis, polymerase chain reaction is useful to detect the genomic DNA for VZV in the aqueous humor and vitreous fluids.^{16,17} Second, it is possible that the reactivation of VZV triggers some immunologic mechanisms, such as changing a tissue antigen or antigenic stimulation, which may later lead to uveitis.^{18,19} Third, keeping latent VZV under control and maintaining the healthy condition of the eye are related to host immunity. Any dysfunction of host immunity can result in the emergence of HZ and uveitis.²⁰ In addition, comorbidities associated with autoimmune diseases may be more frequent. Our results show that RA, psoriasis, SLE, and AS were significantly associated with anterior uveitis during the 1-year follow-up period.

There are several limitations to this study. First, compared with diagnoses obtained through a standardized procedure, diagnoses of HZ and uveitis dependent upon ICD-9-CM codes may be less accurate. This is a major limitation. However, the NHI Bureau in Taiwan interviews patients randomly and reviews medical records every year to confirm the validity of diagnoses and the quality of care by randomly sampling a certain percentage of claims from every hospital. Hospitals face the risk of heavy penalties and ongoing scrutiny if discrepancies or evidence of malpractice are found. Therefore, we supposed that every patient with a diagnosis of HZ and uveitis received a thorough examination in the clinic.

Second, data on some variables that might contribute to the development of uveitis, such as eye injury, were not available in this database. These factors could compromise our findings. Third, some patients with HZ may have chosen not to seek medical help. Because the NHI System in Taiwan allows patients to visit any clinic or hospital freely without referral by a general practitioner, and patients pay only approximately US \$5 to \$15 per visit (in 2004, Taiwan's per capita gross national product was US \$14 093), the barriers to receiving medical help are negligible. Considering the severe symptoms in patients with HZ and the minimal barriers to medical access in Taiwan, we believe most patients with HZ would seek medical help as soon as possible once the disease strikes and that the number of individuals with HZ not seeking medical help would be minimal. This small percentage of individuals with HZ who might not seek medical help would be categorized as non-HZ, so there is a slight chance of being selected as a part of the comparison cohort, diluting real differences in subsequent uveitis incidence between the study and comparison co-

horts. Our survey results show that patients with HZ demonstrated a significantly higher risk of uveitis. Therefore, our finding of an increased incidence of subsequent uveitis in patients with HZ is a true phenomenon.

In addition, most residents of Taiwan are of Chinese ethnicity. When comparing the results of our study with others, differences in study design, race, targeted patients, era of patient collection, and duration of follow-up must be regarded. The ability to generalize our results to other ethnic/racial groups is unclear given that uveitis in Chinese/Asians might not be entirely similar to that in other ethnic groups.

In summary, this nationwide population-based study has demonstrated that HZ may represent a marker of increased risk for subsequent anterior uveitis in the 1-year period after HZ diagnosis. These findings suggest that a patient's intraocular condition should be closely observed in the year following diagnosis with HZ. We hope similar studies elsewhere in the world will determine whether our data can be replicated and used to establish guidelines on the extent to which patients with HZ should be evaluated for anterior uveitis.

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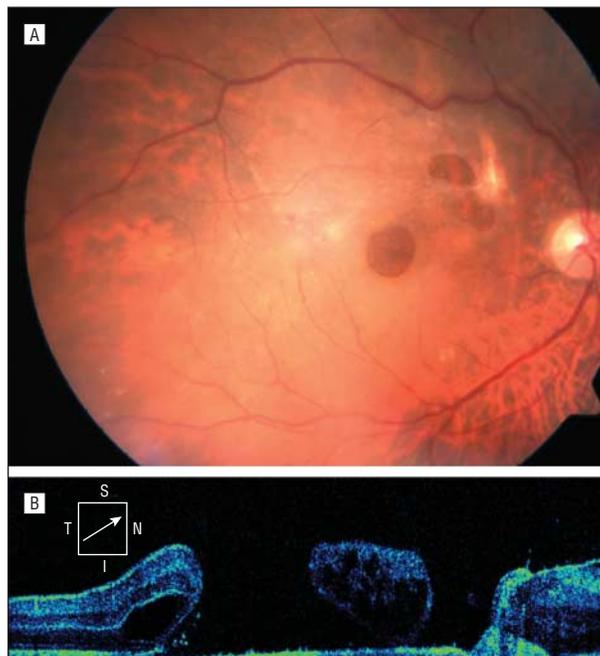
Ophthalmic Images

Multiple Macular Holes

Soumyava Basu, MS

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A 66-year-old man with diminished vision in the right eye for 6 months. A, Fundus photograph of the right eye shows 3 distinct full-thickness macular holes (1 foveal and 2 extrafoveal) associated with an epiretinal membrane. B, Optical coherence tomographic scan confirms the clinical findings. The arrow represents the direction of the scan. I indicates inferior; N, nasal; S, superior; and T, temporal.