Herpes Zoster and Dementia:
A Nationwide Population-Based Cohort Study

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ABSTRACT

Objective: Some infectious diseases have been found to be associated with cognitive impairment and dementia. However, the relationship between herpes zoster and dementia has received little attention. This study aimed to investigate this association as well as associations of antiviral treatments for herpes zoster and incident dementia using a large national sample.

Methods: Cases were identified from the Taiwan National Health Insurance Research Database with a new diagnosis of herpes zoster (*ICD-9-CM* code: 053) between 1997 and 2013. Each identified individual with a case of herpes zoster was compared with 1 sex-, age-, and residence-matched control subject. Both groups were followed until the first diagnosis of dementia (*ICD-9-CM* codes: 290.0 to 290.4, 294.1, 331.0 to 331.2, and 331.82), withdrawal from the registry, or the end of 2013. Cox regression analyses and competing risk model were applied, adjusting for sex, age, residence, depression, autoimmune disease, ischemic stroke, traumatic brain injury, alcohol use disorder, and antiviral treatments for herpes zoster to evaluate the risk of interest.

Results: A total of 39,205 cases with herpes zoster were identified. Of the 78,410 study and comparison subjects, 4,204 were diagnosed as having dementia during a mean (SD) follow-up period of 6.22 (4.05) years. Herpes zoster was associated with a slightly increased risk of dementia in the fully adjusted model (hazard ratio [HR] = 1.11; 95% CI, 1.04–1.17). Prescriptions of antiviral therapy were associated with a reduced risk of developing dementia following the diagnosis of herpes zoster (HR = 0.55; 95% CI, 0.40–0.77).

Conclusions: Herpes zoster was associated with an increased risk of dementia, independent of potential confounding factors. Antiviral treatment might be protective in preventing dementia in patients with herpes zoster.

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Dementia is a major neurocognitive disorder characterized by impaired memory, learning, executive function, perceptual-motor processes, complex attention, social cognition, and language use. Dementia may cause severe disabilities in daily activities, leading to a great health care burden in the general population worldwide. The prevalence of dementia is 5%–7% in people aged older than 60 years,[1] which is approximately 46.8 million people worldwide. With the increasing prevalence of dementia, the total cost of care related to dementia is also rising.[2]

The etiology for dementia is heterogeneous. The main risk factor is aging. Other defined risk factors include the allelic variant of apolipoprotein E ε4, alcohol use, low education level, smoking, Down syndrome, traumatic head injury, depression, inflammatory or autoimmune diseases, and vascular factors such as hypertension, hyperlipidemia, stroke, and diabetes.[3–6] In addition, some infectious diseases are known to be associated with cognitive impairment and dementia, including prion disease, human immunodeficiency virus (HIV), and herpes simplex virus infection (HSV).[7–9] The literature suggests that recurrent HSV type-1 infection can be considered a risk factor for Alzheimer's disease, although there was no evidence of causal relationships between HSV and Alzheimer's disease at the time of preparing this article.[9] However, the risk associations of dementia and another virus in the same group, the varicella-zoster virus (VZV), still remain unclear.

VZV is a human α-herpes virus that causes varicella. Endogenous reactivation of latent VZV infection results in herpes zoster.[10] VZV may affect both the central nervous system (CNS) and the peripheral nervous system and can, despite antiviral treatment, result in neurologic sequelae such as post-herpetic neuralgia after herpes zoster and cognitive sequelae after herpes zoster encephalitis (HZE).[11,12] Previous studies have reported poor cognitive outcomes following HZE, but the sample sizes were small and lacked

Clinical Points

- This population-based cohort study found that the diagnosis of herpes zoster was associated with a significantly increased risk of dementia.
- Prescriptions of antiviral therapy were associated with a reduced risk of dementia and might be protective in preventing the development of dementia following the diagnosis of herpes zoster.

long-term follow-up.[13–15] One follow-up study reported that 5 in 14 patients with VZV infection having CNS involvement later had subsequent diagnosis of mild cognitive impairment (MCI) in domains of speed, attention, learning, memory, and executive function in the 3-year follow-up period, whereas no MCI was found in the comparison group.[15] On the other hand, although antiviral therapy for herpes zoster may accelerate the healing of cutaneous lesions and may decrease the duration and severity of acute neuritis,[16,17] there is insufficient evidence to date as to whether antiviral therapy decreases the risk of post-herpetic neuralgia.[18] Also, while a previous study has reported antiviral therapy as the best predictor of cognitive outcome following HSV encephalitis,[19] no study has evaluated associations of antiviral therapy for VZV infection or herpes zoster and long-term neurocognitive impairments.

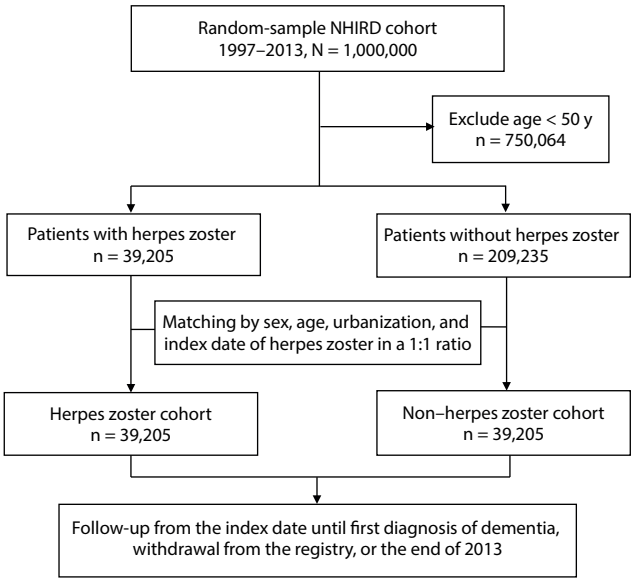
Taking advantage of a nationwide population-based cohort, the present study aims to investigate associations of herpes zoster, antiviral treatments, and incident dementia.

METHODS

Study Design

This research was structured as a population-based, retrospective cohort study. The data source for this study was the National Health Insurance Research Database (NHIRD) of the National Health Insurance (NHI) of Taiwan. The NHI program is a government-run, single-payer mandatory health insurance program that was initiated in 1995 and covers of all forms of medical services. The program covered nearly 99.0% of the population since 1998. The NHIRD was established by the National Health Research Institute of Taiwan in 1997 for scientific and study purposes. The NHIRD is one of the largest nationwide population databases in the world, covering approximately 23 million residents in Taiwan. Comprehensive information on insured individuals is included in the database, such as demographic data, disease diagnoses, dates, and prescriptions or interventions given at each clinical visit. Individual medical records included in the NHIRD are anonymous to protect patient privacy. In cooperation with the Bureau of NHI, the National Health Research Institute extracted a representative database of 1,000,000 people from the year 2005 registry of all NHI enrollees using a systematic random sampling method for research purposes, forming the Longitudinal Health Insurance Database (LHID).[20] There are no statistically significant differences in age, sex, or health care costs between this sample and all enrollees.[20] Disease diagnoses were coded using the *International Classification of Diseases*, Ninth Revision, Clinical Modification (*ICD-9-CM*). Previous studies have demonstrated that validity and accuracy between NHIRD claims data and medical records are moderate to substantial ($\kappa = 0.55–0.95$, with positive predictive values between 0.5 and 1.0).[21–23]

Figure 1. Flowchart of Data Collection in This Study



Abbreviation: NHIRD = National Health Insurance Research Database.

Our study subjects with herpes zoster were identified on the basis of recorded *ICD-9-CM* codes 053.0X to 053.9X. All medical claims made under these diagnostic codes during 1997 and 2013 were collected from NHIRD for further analysis. The definition of herpes zoster for this analysis required at least 1 inpatient and/or outpatient diagnosis.[24] The date of the first diagnosis of herpes zoster was defined as the index date. For the purpose of investigating the association between herpes zoster and dementia, our study excluded those subjects below 50 years of age. One comparison subject per each study subject was randomly sampled from the remaining sample, matching for sex, age within 1 year, residence, and the index date (Figure 1).

Both case subjects and controls were followed for dementia as the main outcome. According to previous systemic review of optimal *ICD* codes to study neurologic conditions, the diagnosis of dementia was defined on the basis of recorded *ICD-9-CM* codes 290.0X to 290.4X, 294.1X, 331.0X to 331.2X, and 331.82 in our study[25] (Table 1). For consistency and certainty of the diagnosis, dementia was identified by diagnosis that was given at least once from inpatient care data and/or 3 times from outpatient care data.[26] Both case subjects and controls were followed for dementia as an outcome. To define new cases of dementia, people who had received any dementia diagnosis in medical claim data before the index date were excluded from the analysis.

Table 1. *ICD-9-CM* Dementia Codes Used in This Study

Code	Diagnosis
290.0	Senile dementia, uncomplicated
290.1	Presenile dementia
290.2	Senile dementia with delusional or depressive features
290.3	Senile dementia with delirium
290.4	Vascular dementia
294.1	Dementia in conditions classified elsewhere
331.0	Alzheimer's disease
331.1	Frontotemporal dementia
331.2	Senile degeneration of brain
331.82	Dementia with Lewy bodies

Risk factors for both herpes zoster and dementia were identified as covariates, including age, depressive disorder (*ICD-9-CM* codes 296.2X, 296.3X, 300.4X, and 311.XX), HSV infection (*ICD-9-CM* code 054), ischemic stroke (*ICD-9-CM* codes 433.0–433.9X, 434.0–434.9X, and 436), traumatic brain injury (*ICD-9-CM* codes 850.0–850.9X, 854.0X, and 959.01), autoimmune disease (*ICD-9-CM* codes 136.1X, 340.XX, 710.0X, 710.2X, 714.0–714.3X, and 446.0X–446.7), and alcohol use disorder (*ICD-9-CM* codes 291.0X–291.9X and 303.0–303.9).[3–7,27,28] All covariates were defined as having the above medical diagnosis at least once from inpatient care data, or on at least 3 occasions from outpatient care data during the entire study period. In addition, antiviral therapy for herpes zoster, including all forms of acyclovir, tromantadine, famciclovir, and valacyclovir, were considered as exposure variables. Information about antiviral treatment was obtained from NHIRD by NHI drug codes. The "prescription of antiviral treatment" was defined as antiviral agents being prescribed no earlier than the index date (the date of first diagnosis of herpes zoster) of each study subject (ie, patients with diagnosis of herpes zoster only).

A sensitivity analysis was conducted for subsamples. In order to leave a latent period to observe whether the chronic progression of dementia was actually after the occurrence of herpes zoster, and not beforehand,[15,27] we performed a sensitivity analysis on those with a duration of 3 years between diagnoses of herpes zoster and dementia. This study was approved by the institutional review board of the Tsaotun Psychiatric Centre.

Statistical Analysis

Distributions between the herpes zoster and control groups were described and compared by the χ^2 test for categorical variables. The index date for each case was the first date of herpes zoster. The year of index date was also assigned for the matching of comparison subject. Survival analysis was applied using the date of dementia, withdrawal from the registry, or the end of 2013 as end points. Cox regression analysis with competing risk model was used to estimate associations of herpes zoster and dementia and to adjust for covariates. Interaction terms for both the incidence and the risk of dementia following herpes zoster treatment were tested. All data management was performed using SAS 9.4 software (SAS Institute Inc, Cary, North Carolina). Calculations of cumulative incidences and Cox models in the competing risk analysis were carried out using the R package "cmprsk."[29]

Table 2. Characteristics of Herpes Zoster Case Subjects and Their Matched Controls[a]

Characteristic	Herpes Zoster (n = 39,205)	Non–Herpes Zoster (n = 39,205)	χ^2 Test *P* Value
Sex			
Female	21,422 (54.64)	21,422 (54.64)	1.000
Male	17,783 (45.36)	17,783 (45.36)	
Age at entry, mean (SD), y	63.54 (10.00)	63.5 (10.00)	
50–59	16,702 (42.60)	16,702 (42.60)	1.000
60–69	11,284 (28.78)	11,284 (28.78)	
70–79	8,354 (21.31)	8,354 (21.31)	
80–89	2,617 (6.68)	2,617 (6.68)	
≥ 90	248 (0.63)	248 (0.63)	
Residence			
1 (most urbanized)	11,627 (29.66)	11,627 (29.66)	1.000
2	17,381 (44.33)	17,381 (44.33)	
3	6,646 (16.95)	6,646 (16.95)	
4 (most rural)	3551 (9.06)	3,551 (9.06)	
Depression[b]			
No	34,768 (88.68)	35,537 (90.64)	<.0001
Yes	4,437 (11.32)	3,668 (9.36)	
Autoimmune disease[b]			
No	36,506 (93.12)	37,337 (95.24)	<.0001
Yes	2,699 (6.88)	1,868 (4.76)	
Ischemic stroke[b]			
No	33,460 (85.35)	33,825 (86.28)	<.0001
Yes	5,745 (14.65)	5,380 (13.72)	
Traumatic brain injury[b]			
No	36,266 (92.50)	36,498 (93.10)	.001
Yes	2,939 (7.50)	2,707 (6.90)	
Alcohol use disorder[b]			
No	36,106 (92.10)	36,326 (92.66)	.003
Yes	3,099 (7.90)	2,879 (7.34)	
Herpes simplex virus infection[b]			
No	38,882 (99.18)	39,069 (99.65)	<.0001
Yes	323 (0.82)	136 (0.35)	
Herpes zoster drug[c]			
No	37,074 (94.56)	38,998 (99.47)	<.0001
Yes	2,131 (5.44)	207 (0.53)	
Dementia[d]			
No	37,031 (94.45)	37,175 (94.82)	.022
Yes	2,174 (5.55)	2,030 (5.18)	
Follow-up, mean (SD), y	6.08 (4.05)	6.35 (4.04)	<.0001

[a]Values shown as n (%) unless otherwise noted.
[b]Whole period.
[c]Herpes zoster drug prescribed on or after the index date.
[d]Dementia diagnosed after the index date.

RESULTS

Subject Characteristics

Two cohorts comprised 39,205 people with newly diagnosed herpes zoster and 39,205 matched comparison subjects from the database for the period 1997–2013. Cohort characteristics are listed and compared in Table 2. Mean (SD) follow-up intervals were 6.08 (4.05) years for the herpes zoster cohort and 6.35 (4.04) years for the non–herpes zoster cohort. Among the herpes zoster case subjects, a small majority were male, and most subjects were aged between 50 and 59 years. Of the total 78,410 subjects, 4,204 received a diagnosis of dementia during the surveillance period: 2,174 (5.55%) in the herpes zoster cohort and 2,030 (5.18%) in the non–herpes zoster cohort. In the herpes zoster cohort, 2,131 (5.44%) received antiviral therapy at and/or after the index date. The proportion of depression, HSV infection, autoimmune disease, ischemic stroke, traumatic brain injury, and alcohol use disorder

Table 3. Cox Regression Analysis of Dementia Incidence

		Unadjusted			Adjusted[a]		
Variable	n	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Herpes zoster							
No	39,205	1.00			1.00		
Yes	39,205	1.12	1.06–1.19	.000	1.11	1.04–1.17	.0014
Sex							
Female	42,844	1.00			1.00		
Male	35,566	0.97	0.91–1.03	.319	0.83	0.78–0.88	<.0001
Age at entry, y							
50–59	23,254	1.00			1.00		
60–69	22,568	4.90	4.26–5.64	<.0001	4.32	3.75–4.97	<.0001
70–79	16,708	14.36	12.59–16.38	<.0001	10.71	9.37–12.24	<.0001
80–89	5,234	28.06	24.46–32.19	<.0001	18.22	15.83–20.96	<.0001
≥90	496	36.68	29.40–45.77	<.0001	25.32	20.26–31.64	<.0001
Residence							
1 (most urbanized)	23,254	0.70	0.62–0.77	<.0001	0.91	0.82–1.01	.0799
2	34,762	0.77	0.70–0.85	<.0001	0.97	0.88–1.07	.5511
3	13,292	0.92	0.82–1.03	.151	0.96	0.86–1.08	.5044
4 (most rural)	7,102	1.00			1.00		
Depression[b]							
No	70,305	1.00			1.00		
Yes	8,105	2.96	2.76–3.17	<.0001	1.19	1.10–1.29	<.0001
Autoimmune disease[b]							
No	73,843	1.00			1.00		
Yes	4,567	1.38	1.24–1.55	<.0001	1.11	0.99–1.25	.0633
Ischemic stroke[b]							
No	67,285	1.00			1.00		
Yes	11,125	4.44	4.18–4.72	<.0001	2.05	1.92–2.18	<.0001
Traumatic brain injury[b]							
No	72,764	1.00			1.00		
Yes	5,646	1.95	1.79–2.13	<.0001	1.24	1.14–1.36	<.0001
Alcohol use disorders[b]							
No	72,432	1.00			1.00		
Yes	5,978	8.08	7.59–8.60	<.0001	5.16	4.80–5.54	<.0001
Herpes simplex virus[b]							
No	77,951	1.00			1.00		
Yes	459	0.69	0.44–1.08	.1081	0.66	0.42–1.03	.0687
Herpes zoster drug[c]							
No	76,072	1.00			1.00		
Yes	2,338	0.46	0.33–0.62	<.0001	0.54	0.39–0.73	<.0001

[a]Adjusted for sex, age, residence, depression, autoimmune disease, ischemic stroke, traumatic brain injury, alcohol use disorder, antiviral treatments, herpes simplex virus infection, and herpes zoster drug.
[b]Whole period.
[c]Herpes zoster drug prescribed on or after the index date.
Abbreviation: HR = hazard ratio.

before the end of follow-up was higher in the herpes zoster cohort than in the non–herpes zoster cohort.

Association Between Herpes Zoster and Dementia

Analyses of associations of interest are summarized in Table 3. The cumulative incidence of dementia in the herpes zoster cohort remained higher than in the non–herpes zoster cohort during a mean follow-up period of 6.2 years with an unadjusted hazard ratio (HR) of 1.12 (95% CI, 1.06–1.19). After adjustments for a range of potential confounding factors, including age group, residence, depression, HSV infection, autoimmune disease, ischemic stroke, traumatic brain injury, alcohol use disorder, and antiviral drugs, the associations with dementia in the herpes zoster group remained higher than in the comparison subjects (adjusted HR: 1.11; 95% CI, 1.04–1.17). Additional factors associated with the incidence of dementia were female sex, older age, depression, ischemic stroke, traumatic brain injury, alcohol use disorder, and absence of antiviral drugs. Interaction terms were significant for herpes zoster × depression (HR: 1.29; 95% CI 1.16–1.43; interaction $P = .046$), herpes zoster × alcohol use disorder (HR: 5.57, 95% CI, 5.06–6.14; $P < .001$), and antiviral drugs × female sex (HR: 0.40; 95% CI, 0.25–0.66; $P = .038$).

Secondary analyses involving antiviral medications within the herpes zoster cohort are described in Table 4. The mean (SD) treatment periods among outpatients with diagnosis of VZV infection were 17.12 (36.12) days, with a median value of 12 days. In the herpes zoster cohort, treatment with antiviral agents significantly reduced the risk of developing dementia with a crude HR of 0.47 (95% CI, 0.34–0.65) and an adjusted HR of 0.55 (95% CI, 0.40–0.77).

Results from the sensitivity analysis including only patients with a 3-year latent period from index date to the date of dementia were similar to our main finding. The herpes zoster cohort was associated with a slightly higher risk of dementia (HR, 1.08; 95% CI, 1.00–1.16) than the non–herpes zoster cohort. Antiviral therapy was still associated with a significantly reduced risk (adjusted HR, 0.49; 95% CI, 0.31–0.77).

DISCUSSION

To our knowledge, this is the first study using a nationally representative sample and longitudinal dataset to investigate the relationship between herpes zoster and dementia. After adjusting for sex, age group, residence, depression, HSV infections, autoimmune disease, ischemic stroke, traumatic brain injury, alcohol use disorder, and antiviral drugs, we found the risk of dementia was slightly higher in patients with herpes zoster (adjusted HR: 1.11; 95% CI, 1.04–1.17). In the herpes zoster study cohort, treatment with antiviral drugs was associated with a reduced risk of developing dementia, with an adjusted HR of 0.56 (95% CI, 0.40–0.77). We suggest that receiving antiviral treatment might be a protective factor for dementia and that this issue deserves further research investigation.

Herpes Zoster and Dementia

Our results of increased incidence of dementia following herpes zoster were in line with previous studies revealing more neuropsychological sequelae or incident MCI following VZV CNS infection or HZE compared to normal controls.[13–15] Since information about clinical symptoms was unavailable from the NHIRD, we are unable to comment upon whether or not having CNS symptoms at presentation was

Table 4. Cox Regression Analysis of Dementia Incidence Among Case Subjects With Herpes Zoster

		Unadjusted			Adjusted[a]		
Variable	n	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Herpes zoster drug[b]							
No	37,074	1.00			1.00		
Yes	2,131	0.47	0.34–0.65	<.0001	0.55	0.40–0.77	.0004
Sex							
Female	21,422	1.00			1.00		
Male	17,783	0.95	0.87–1.03	.209	0.82	0.75–0.89	<.0001
Age at entry, y							
50–59	16,702	1.00					
60–69	11,284	5.09	4.20–6.17	<.0001	1.00		
70–79	8,354	14.06	11.72–16.85	<.0001	4.54	3.74–5.50	<.0001
80–89	2,617	27.79	22.99–33.58	<.0001	10.66	8.87–12.81	<.0001
≥ 90	248	37.05	27.22–50.44	<.0001	18.32	15.10–22.23	<.0001
Residence							
1 (most urbanized)	11,627	0.70	0.60–0.81	<.0001	0.91	0.79–1.06	.2371
2	17,381	0.75	0.65–0.86	<.0001	0.94	0.81–1.08	.362
3	6,646	0.92	0.79–1.08	.317	0.98	0.84–1.14	.7729
4 (most rural)	3,551	1.00			1.00		
Depression[c]							
No	34,768	1.00			1.00		
Yes	4,437	2.76	2.51–3.04	<.0001	1.20	1.08–1.34	.0008
Autoimmune disease[c]							
No	36,506	1.00			1.00		
Yes	2,699	1.41	1.22–1.63	<.0001	1.16	1.00–1.34	.0459
Ischemic stroke[c]							
No	33,460	1.00			1.00		
Yes	5,745	4.28	3.94–4.67	<.0001	2.01	1.84–2.20	<.0001
Traumatic brain injury[c]							
No	36,266	1.00			1.00		
Yes	2,939	1.87	1.66–2.11	<.0001	1.13	1.00–1.28	.0499
Alcohol use disorders[c]							
No	36,106	1.00			1.00		
Yes	3,099	7.25	6.65–7.91	<.0001	4.76	4.31–5.26	<.0001
Herpes simplex virus[c]							
No	38,882	1.00			1.00		
Yes	323	0.67	0.40–1.13	.1346	0.91	0.60–1.38	.6533

[a]Adjusted for sex, age, residence, depression, autoimmune disease, ischemic stroke, traumatic brain injury, alcohol use disorder, antiviral treatments, herpes zoster drug, and herpes simplex virus infections.
[b]Herpes zoster drug prescribed on or after the index date.
[c]Whole period.
Abbreviation: HR = hazard ratio.

associated with subsequent neurologic sequelae. However, CNS symptoms such as multiple cognitive impairments, greater brain atrophy than expected, or resting state whole brain and hippocampal hypoperfusion have been reported to be associated with the outcome of dementia following herpes zoster.[15,30] Subclinical abnormalities on magnetic resonance imaging (MRI) of brain and cerebrospinal fluid (CSF) occurring in patients with herpes zoster without CNS symptoms were also observed.[31] In addition, herpes zoster patients with abnormal MRI findings were found to be at risk for developing postherpetic neuralgia.[31] These associations might have indicated that if a patient presented with CNS symptoms, further imaging or CSF studies should be considered for predicting and detecting the risk of subsequent neurologic sequelae, particularly when early identification and treatment might help preserving cognitive functions.

A probable mechanism for association between herpes zoster and dementia might presumably be direct virus invasion into the brain, though CNS symptoms at initial presentation may be lacking.[31] Research has shown that inflammatory changes, intrathecal anti-VZV antibodies, or VZV DNA found on pathologic or CSF studies from areas outside the cutaneous lesions, spinal cord, meninges, or the brain might suggest blood-brain barrier damage or virus traveling centripetally.[31–34] Such CNS involvements might have contributed to the development of dementia. Besides the route of direct CNS invasion, VZV infection was also associated with induction of systemic inflammatory cytokines, including tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6), produced by human monocytes and macrophages via Toll-Like receptor 2.[35] Prior studies have reported that inflammatory markers such as TNF-α, IL-6, and C-reactive protein (CRP) are increased before clinical onset of dementia, including Alzheimer disease and vascular dementia.[36,37] A recent meta-analysis reported that higher CRP and IL-6 levels were associated with a modestly greater risk of all-cause dementia.[38] It should be noted that, through the systemic inflammatory mechanism, initial CNS presentation might be asymptomatic.[31] Pathways of viral extensions into CNS, or systemic inflammatory responses leading to neuropsychological sequelae, including predispositions of dementia, still require further investigation.

The other possible mechanism that might explain associations between herpes zoster and dementia is VZV-induced vasculopathy. VZV is the only human virus that has been shown to replicate in arteries and produce disease.[39] With VZV infections in both small and large arteries in the brain, VZV-induced vasculopathy might lead to ischemic as well as hemorrhagic stroke, aneurysm, dissection, and venous sinus thrombosis.[39] A previous self-controlled case-series study of 6,584 individuals with herpes zoster reported an increased rate of stroke within 6 months following zoster, and oral antiviral therapy was associated with a decreased risk of stroke.[40] Since stroke-related vascular dementia is known to be the second most common cause of acquired cognitive impairment and dementia,[41] we suggest that cerebrovascular diseases associated with VZV vasculopathy might be a potential mechanism for the raised risk of dementia in the herpes zoster cohort. Although we have adjusted for ischemic stroke as a confounding factor, there might still be other subclinical VZV viral effects or other unknown mechanisms on the brain that need further clarification.[39]

In our study, the finding that the risk of dementia was reduced in the subgroup of people receiving antiviral agents compared to those untreated was comparable to the finding of a previous case report of VZV multifocal vasculopathy, manifesting

multi-infarct dementia. That study described improvements in mental status and gait after intravenous acyclovir was given, and such improvements persisted even after 26 months.[42] It is known that antiviral drugs reduce acute pain and zoster severity, accelerate healing, and may reduce post-herpetic neuralgia.[16] Antiviral drugs might have the potential to reduce post-zoster adverse events by reducing inflammation.[17] In addition, previous research also showed improved vessel wall thickening and decreased enhancement in 4 of 6 patients via high-resolution MRI after antiviral treatment of VZV intracranial vasculopathy.[43] A large case-series study has also reported that the risk of stroke was reduced in zoster patients who received oral antiviral therapy compared to those who were untreated.[40] However, since literature evaluating the effect of antiviral therapy on neurocognitive outcomes in the patient with herpes zoster was scarce, further replications or research are still required.

Strengths and Limitations

This study is the first using a nationwide representative sample and longitudinal dataset to investigate the possible causal relationship between herpes zoster and dementia. Our study is also the first to evaluate associations between antiviral therapy for herpes zoster and the risk of developing dementia. Nonetheless, there are also important limitations. First, the sample size in patients receiving antiviral treatment is smaller than the study cohort. However, the power for this sample size is within acceptable range (power = 0.89), and therefore the result is trustworthy. Second, the information contained in this large database from NHIRD was not as comprehensive as that obtained from individuals' medical records. Therefore, it was not possible to directly evaluate the severity, involvement, and complication of herpes zoster in our study. Third, it might be possible that these antiviral agents were prescribed for treating other diseases, such as HSV, or for long-term prophylactic use instead of short-term treatment. However, we defined our exposure status for antiviral treatment as no earlier than the index date of first diagnosis of herpes zoster among our study subjects with a main diagnosis of herpes zoster and that the average treatment period was rather short (17 days). Hence, we believe the majority of such prescriptions were for short-term treatment. Finally, this study lacks information on other potential confounders such as family history of dementia, genetic factors, lifestyle, or cardio-metabolic factors of each patient.

CONCLUSION

Our findings from a national health insurance data set showed a slightly positive association between herpes zoster and dementia. More importantly, antiviral therapy may lead to a reduction in the risk of developing dementia following herpes zoster. Given the increased prevalence of dementia and its negative impacts on quality of life, it is imperative to prevent cognitive deterioration and dementia. Therefore, the importance of prescribing antiviral drugs in the treatment of herpes zoster may be in terms not only of reducing zoster severity in the acute phase, but also of preventing post-zoster neurocognitive adverse events. Further research is still warranted for the explorations of underlying mechanisms.

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REFERENCES

1. Prince M, Bryce R, Albanese E, et al. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement*. 2013;9(1):63–75.e2.
2. World Alzheimer Report 2015—The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends. Alzheimer's Disease International website. https://www.alz.co.uk/research/worldalzheimerreport2015summary.pdf. 2015.
3. Mayeux R. Epidemiology of neurodegeneration. *Annu Rev Neurosci*. 2003;26:81–104.
4. Dregan A, Chowienczyk P, Gulliford MC. Are inflammation and related therapy associated with all-cause dementia in a primary care population? *J Alzheimers Dis*. 2015;46(4):1039–1047.
5. Wallin K, Solomon A, Kåreholt I, et al. Midlife rheumatoid arthritis increases the risk of cognitive impairment two decades later: a population-based study. *J Alzheimers Dis*. 2012;31(3):669–676.
6. Staff NP, Lucchinetti CF, Keegan BM. Multiple sclerosis with predominant, severe cognitive impairment. *Arch Neurol*. 2009;66(9):1139–1143.
7. Heaton RK, Clifford DB, Franklin DR Jr, et al; CHARTER Group. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology*. 2010;75(23):2087–2096.
8. Tousseyn T, Bajsarowicz K, Sánchez H, et al. Prion disease induces Alzheimer disease-like neuropathologic changes. *J Neuropathol Exp Neurol*. 2015;74(9):873–888.
9. Piacentini R, De Chiara G, Li Puma DD, et al. HSV-1 and Alzheimer's disease: more than a hypothesis. *Front Pharmacol*. 2014;5:97.
10. Straus SE, Ostrove JM, Inchauspé G, et al. NIH conference, varicella-zoster virus infections: biology, natural history, treatment, and prevention. *Ann Intern Med*. 1988;108(2):221–237.
11. Persson A, Bergström T, Lindh M, et al. Varicella-zoster virus CNS disease—viral load, clinical manifestations and sequels. *J Clin Virol*. 2009;46(3):249–253.
12. Appelbaum E, Kreps SI, Sunshine A. Herpes zoster encephalitis. *Am J Med*. 1962;32:25–31.
13. Wetzel K, Asholt I, Herrmann E, et al. Good cognitive outcome of patients with herpes zoster encephalitis: a follow-up study. *J Neurol*. 2002;249(11):1612–1614.
14. Hokkanen L, Launes J, Poutiainen E, et al. Subcortical type cognitive impairment in herpes zoster encephalitis. *J Neurol*. 1997;244(4):239–245.
15. Grahn A, Nilsson S, Nordlund A, et al. Cognitive impairment 3 years after neurological Varicella-zoster virus infection: a long-term case control study. *J Neurol*. 2013;260(11):2761–2769.
16. Jackson JL, Gibbons R, Meyer G, et al. The effect of treating herpes zoster with oral acyclovir in preventing postherpetic neuralgia: a meta-analysis. *Arch Intern Med*. 1997;157(8):909–912.

17. Dworkin RH, Johnson RW, Breuer J, et al. Recommendations for the management of herpes zoster. *Clin Infect Dis*. 2007;44(suppl 1):S1–S26.
18. Li Q, Chen N, Yang J, et al. Antiviral treatment for preventing postherpetic neuralgia. *Cochrane Database Syst Rev*. 2009;(2):CD006866.
19. Kaplan CP, Bain KP. Cognitive outcome after emergent treatment of acute herpes simplex encephalitis with acyclovir. *Brain Inj*. 1999;13(11):935–941.
20. Institutes NHR. Introduction to the National Health Insurance Research Database (NHIRD), Taiwan. 2013. http://nhird.nhri.org.tw/date_01_en.html. Accessed June 20, 2016.
21. Chang L. *A Study of Validation on Comorbidity Derived From Claims Data*. Taiwan: National Yang-Ming University; 2004.
22. Cheng CL, Kao YHY, Lin SJ, et al. Validation of the National Health Insurance Research Database with ischemic stroke cases in Taiwan. *Pharmacoepidemiol Drug Saf*. 2011;20(3):236–242.
23. Cheng CL, Lee CH, Chen PS, et al. Validation of acute myocardial infarction cases in the national health insurance research database in Taiwan. *J Epidemiol*. 2014;24(6):500–507.
24. Liu YC, Yang YH, Hsiao HH, et al. Herpes zoster is associated with an increased risk of subsequent lymphoid malignancies—a nationwide population-based matched-control study in Taiwan. *BMC Cancer*. 2012;12:503.
25. Bharmal MF, Weiner M, Sands LP, et al. Impact of patient selection criteria on prevalence estimates and prevalence of diagnosed dementia in a Medicaid population. *Alzheimer Dis Assoc Disord*. 2007;21(2):92–100.
26. Wu KY, Chang CM, Liang HY, et al. Increased risk of developing dementia in patients with bipolar disorder: a nested matched case-control study. *Bipolar Disord*. 2013;15(7):787–794.
27. Chen MH, Wei HT, Su TP, et al. Risk of depressive disorder among patients with herpes zoster: a nationwide population-based prospective study. *Psychosom Med*. 2014;76(4):285–291.
28. Zhang JX, Joesoef RM, Bialek S, et al. Association of physical trauma with risk of herpes zoster among Medicare beneficiaries in the United States. *J Infect Dis*. 2013;207(6):1007–1011.
29. Gray B. cmprsk: Subdistribution analysis of competing risks. 2014. https://cran.r-project.org/web/packages/cmprsk/index.html. Accessed June 20, 2016.
30. Bangen KJ, Delano-Wood L, Wierenga CE, et al. Dementia following herpes zoster encephalitis. *Clin Neuropsychol*. 2010;24(7):1193–1203.
31. Haanpää M, Dastidar P, Weinberg A, et al. CSF and MRI findings in patients with acute herpes zoster. *Neurology*. 1998;51(5):1405–1411.
32. Puchhammer-Stöckl E, Popow-Kraupp T, Heinz FX, et al. Detection of varicella-zoster virus DNA by polymerase chain reaction in the cerebrospinal fluid of patients suffering from neurological complications associated with chicken pox or herpes zoster. *J Clin Microbiol*. 1991;29(7):1513–1516.
33. Gilden DH, Beinlich BR, Rubinstien EM, et al. Varicella-zoster virus myelitis: an expanding spectrum. *Neurology*. 1994;44(10):1818–1823.
34. Schädlich H-J, Nekic M, Jeske J, et al. Intrathecal humoral immune reaction in zoster infections. *J Neurol Sci*. 1991;103(1):101–104.
35. Wang JP, Kurt-Jones EA, Shin OS, et al. Varicella-zoster virus activates inflammatory cytokines in human monocytes and macrophages via Toll-like receptor 2. *J Virol*. 2005;79(20):12658–12666.
36. Tan ZS, Beiser AS, Vasan RS, et al. Inflammatory markers and the risk of Alzheimer disease: the Framingham Study. *Neurology*. 2007;68(22):1902–1908.
37. Engelhart MJ, Geerlings MI, Meijer J, et al. Inflammatory proteins in plasma and the risk of dementia: the Rotterdam Study. *Arch Neurol*. 2004;61(5):668–672.
38. Koyama A, O'Brien J, Weuve J, et al. The role of peripheral inflammatory markers in dementia and Alzheimer's disease: a meta-analysis. *J Gerontol A Biol Sci Med Sci*. 2013;68(4):433–440.
39. Nagel MA, Gilden D. Developments in Varicella zoster virus vasculopathy. *Curr Neurol Neurosci Rep*. 2016;16(2):12.
40. Langan SM, Minassian C, Smeeth L, et al. Risk of stroke following herpes zoster: a self-controlled case-series study. *Clin Infect Dis*. 2014;58(11):1497–1503.
41. O'Brien JT, Erkinjuntti T, Reisberg B, et al. Vascular cognitive impairment. *Lancet Neurol*. 2003;2(2):89–98.
42. Silver B, Nagel MA, Mahalingam R, et al. Varicella zoster virus vasculopathy: a treatable form of rapidly progressive multi-infarct dementia after 2 years' duration. *J Neurol Sci*. 2012;323(1–2):245–247.
43. Cheng-Ching E, Jones S, Hui FK, et al. High-resolution MRI vessel wall imaging in varicella zoster virus vasculopathy. *J Neurol Sci*. 2015;351(1–2):168–173.

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