

## Increased risk of dementia following herpes zoster ophthalmicus

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*PLoS ONE*. 12.11 (Nov. 22, 2017): pe0188490.

DOI: <http://dx.doi.org.york.ezproxy.cuny.edu/10.1371/journal.pone.0188490>

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Full Text:

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### Introduction

Dementia is a clinical syndrome caused by damage to cerebral nerve cells and is characterized by a decline in mental ability severe enough to interfere with daily life [1]. Epidemiological studies have identified many common cardiovascular risk factors for dementia, such as age, diabetes mellitus, smoking, hypercholesterolemia, physical inactivity, increased fat intake, metabolic syndrome, and hypertension. Previous studies also reported evidence of considerable cerebrovascular pathology in Alzheimer's disease (AD). The toxic effects of vascular factors on the brain microvasculature may cause cerebral hypoperfusion and ischemia resulting in angiogenesis, which synergizes with [beta]-amyloid to produce AD [1-9].

Varicella zoster virus (VZV) is the only human virus that can replicate in cerebral arteries and produce vasculopathy, mainly in the elderly and immunocompromised patients [10,11]. The virus spreads transaxonally to cerebral arteries from the trigeminal nerve, particularly from the ophthalmic branch of trigeminal afferent fibers and induces further vascular inflammation and thrombosis that can subsequently injure brain cells [12-14]. Previous reports established that VZV vasculopathy potentially results in transient ischemic attacks, ischemic or hemorrhagic stroke, aneurysms, venous sinus thromboses, and arterial dissection [11,13]. Thus, an increased risk of dementia following VZV vasculopathy or cerebral arteritis with subsequent brain cells damage is a reasonable hypothesis.

Furthermore, previous studies found that among all types of herpes zoster, patients with herpes zoster ophthalmicus (HZO) had a more-marked risk of stroke and vasculopathy than other types of herpes zoster [11-13,15-17]. Several studies also reported that a stroke increases the risk of dementia [18-20]. HZO may therefore be considered a common risk factor in the pathogenesis of dementia and VZV vasculopathy. However, the association between HZO and dementia remains unclear. This retrospective cohort study aimed to

examine the relationship between HZO and the subsequent risk of dementia using a population-based database.

## Methods

### Database

We retrieved the study sample for this retrospective cohort study from the Taiwan Longitudinal Health Insurance Database 2005 (LHID2005). The LHID2005 includes medical claims of healthcare services for 1,000,000 enrollees who were systematically and randomly selected from all enrollees ( $n = 25.68$  million) listed in the 2005 Registry of Beneficiaries under the Taiwan's National Health Insurance (NHI) program. The LHID2005 allows researchers in Taiwan to longitudinally follow-up medical services for these 1,000,000 enrollees since initiation of the NHI in 1995.

This study was approved by the joint institutional review board (JIRB) of Taipei Medical University (TMU-JIRB 201702027).

### Study sample

This study was designed to include a study group and a comparison group. We selected the study group by first identifying 1389 patients who had received a first-time principal diagnosis code of HZO (ICD-9-CM codes 053.2, 053.20, 053.21, 053.22, or 053.29) in clinics or in hospitals between January 1, 2001 and December 31, 2008. We excluded 437 sampled patients who were aged <40 years because of the very low incidence of dementia in this age group. We then assigned the date of receiving their first-time diagnosis of HZO as the index date. We further excluded 70 sampled patients who had a history of major psychosis or a substance-related disorder (ICD-9-CM codes 291~299 or 303~305) prior to the index date. We also excluded 36 sampled patients who had a history of dementia (ICD-9-CM codes 290.0~290.4, 294.1, 331.0~331.2, or 331.82) before the index date. As a result, 846 patients with HZO were included in the study group.

As to the selection of the comparison group, we likewise selected comparison patients from the remaining enrollees in the registry of beneficiaries of the LHID2005. We used propensity score matching to select 2538 comparison patients (three for every study patient with HZO). The selected variables including age, sex, monthly income, geographic location, urbanization level, the year of the index date, hypertension, diabetes, hyperlipidemia, coronary heart disease, and stroke were entered into a multivariable logistic regression model as predictors to calculate the expected probability of receiving a diagnosis of HZO for each patient. In this study, the year of the index date was the year in which patients had received their first-time diagnosis of HZO. Comparison patients were selected by matching them to a given patient with HZO simply on their utilization of medical services in the same index year of that

particular case. We further assigned the first use of medical services in the index year as the index date for the comparison group. We assured that all selected comparison patients had not received a diagnosis of herpes zoster within 1 year before the index date. Furthermore, we assured that none of the selected comparison patients had a history of major psychosis, substance-related disorder, or dementia prior to their index date.

There were 3384 sampled patients including 846 study patients and 2538 comparison patients. Each patient was individually followed for a 5-year period starting from their index date to identify those patients who subsequently received a diagnosis of dementia. To avoid issues associated with the diagnostic validity of the administrative dataset, this study only include patients diagnosed with dementias by a certified neurologist. In addition, dementia cases only included those patients who had received two or more dementia diagnoses.

## **Statistical analysis**

All statistical analyses were performed with SAS statistical software and the significance level was set to 0.05 in this study. We performed a Cox proportional hazards regression to calculate hazard ratios (HRs) along with 95% confidence intervals (CIs) for dementia during the 5-year follow-up period between patients with HZO and comparison patients. The proportional hazards assumption was tested, and we found that survival curves for both strata (patients with HZO and comparison patients) had hazard functions that were proportional over time. In this study, we also censored patients who died or were lost to follow-up during the 5-year follow-up period (155 from the study cohort (18.3% of patients with HZO) and 428 from the comparison cohort (16.9% of comparison subjects)).

## **Results**

Of the study sample, the mean age at the index date was 61.6 years with a standard deviation of 13.1 years; mean ages were 62.2 ( $\pm 12.5$ ) years for patients with HZO and 61.4 ( $\pm 13.3$ ) years for comparison patients ( $p = 0.112$ ). Table 1 shows that there was no significant difference in sex, age, urbanization level and geographic location of patients' residences, monthly income, hypertension, diabetes, hyperlipidemia, coronary heart disease, and stroke between patients with HZO and comparison patients.

Incidence rates of dementia within the 5-year period following their index dates are presented in Table 2. The incidence rate of dementia was 5.24 (95% CI: 4.61~6.51) per 1000 person-years among all sampled patients; respective incidence rates of dementia per 1000 person-years were 10.15 (95% CI: 7.22~13.87) and 3.61 (95% CI: 2.61~4.89) for patients with HZO and comparison patients. Furthermore, the log-rank test indicated that there was a statistically significant difference in 5-year dementia-free accumulated survival rates between patients with HZO and comparison patients ( $p < 0.001$ ).

Table 2 also analyzes HRs for dementia during the 5-year follow-up period for patients with HZO and comparison patients. The Cox proportional analysis showed that the crude HR of dementia during the 5-year follow-up period was 2.83 (95% CI: 1.83~4.37) for patients with HZO compared to comparison patients, after censoring those who died and were lost to follow-up during the follow-up period. Additionally, the covariate-adjusted HR of dementia was 2.97 (95% CI: 1.90-4.67) for patients with HZO compared to comparison patients after adjusting for sex, age, urbanization level and geographic location of patients' residences, monthly income, hypertension, diabetes, hyperlipidemia, coronary heart disease, and stroke (Table 3).

**Table 3. Covariate-adjusted hazard ratios (HRs) for the occurrence of dementia during the 5-year follow-up period among patients with herpes zoster ophthalmicus. [see PDF for image]**

Furthermore, the issue of surveillance bias might have occurred in this study, because many researchers consider that patients with HZO have a greater tendency to receive neurological examinations, and therefore more dementia cases would be detected. We performed a sensitivity analyses by excluding patients who received a diagnosis of dementia within 2 months after their index date ( $n = 4$ ) in order to address this concern. We found that the results remained the same (crude HR = 2.82, 95% CI = 1.80-4.41) (data not shown). The potential surveillance bias thus likely did not compromise the relationship between HZO and dementia reported in this study.

Table 4 further analyzes HRs of dementia between patients with HZO and comparison patients by sex. We found that of the sampled male patients, the crude HR of dementia for patients with HZO was as high as 3.35 (95% CI = 1.79-6.28) compared to comparison patients. In addition, the covariate-adjusted HR of dementia for patients with HZO was 3.41 (95% CI = 1.78-6.53) compared to comparison patients.

## Discussion

This retrospective cohort study showed that 4.61% of the patients with HZO subsequently received a diagnosis of dementia during the 5-year follow-up period compared to 1.65% of patients without HZO. The Cox proportional hazard regression analysis showed that HZO was significantly associated with an increased risk of subsequent dementia (crude HR = 2.83, 95% CI = 1.83-4.37). The high incidence of dementia among HZO patients may be explained by VZV vasculopathy with damage to cerebral neural cells due to cerebral arterial inflammatory and thrombotic responses, which may be a factor leading to dementia [10-16]. Previous studies demonstrated that patients with HZO had higher risks of VZV vasculopathy and stroke than did patients with other types of herpes zoster [15-17]. Studies also mentioned increases in dementia after a stroke, ranging 3%~19% in variable follow-up periods (from 3 months to 10 years) [18-20]. In addition, psychological stress, aging, a poor

social support environment, and adverse life events may contribute to both VZV reactivation and dementia [1-3,21-23].

Some studies suggested that gender is associated with dementia, but their conclusions which only focused on vascular dementia do not permit unequivocal conclusions [3,5,24-25]. In a large population-based prospective cohort study, Ruitenberg et al. reported that the incidence of vascular dementia was higher for men than women in all age groups [26]. In our study, we found that the magnitude of dementia risk following HZO was about 1.4 times as high for males compared to females (crude HR = 3.35 vs. 2.40). The mechanism remains unclear, but it may imply that cerebrovascular events play an important role in HZO with dementia. Previous studies reported that stroke is more common in men, which may be explained by the protective effect of estrogen in premenopausal females and the higher risk of cardiovascular diseases in males [27-29]. Förster et al. reported that diseases of large and small vessels are major causes of male stroke compared to cardioembolism in female stroke victims [29]. This parallels VZV vasculopathy following trigeminal-distribution zoster involving large and small arteries ultimately leading to cerebral infarction, which suggests that males with HZO are at a higher risk of stroke and subsequent dementia than females [11].

This study has several strengths. First, a population-based dataset with a large sample size was used to explore the relationship between HZO and dementia during the study period. The large sample size afforded a considerable statistical advantage in detecting real differences between the two cohorts. Second, the diagnosis of HZO and dementia by certified neurologists, infection specialists, and dermatologists has very high validity in Taiwan.

Nevertheless, the results of this study need to be seen in the light of several limitations. The first limitation is that the LHID 2005 provides no information on the history of smoking, body mass index, education, or alcohol consumption, which are considered to be risk factors and may influence the pathogenesis of dementia [3,4]. This limitation may affect the actual association between HZO and following dementia and may make the relevant analyses incomplete. Second, the absence of a skin rash is well known in VZO- and VZV-related neurological diseases, and because physicians may find it difficult to diagnose such cases, they were not included in our study [30]. Finally, we did not compare the effect of antiviral treatment for HZO with subsequent dementia. However, one study by Lin et al. reported that there was no significant difference in the rate of stroke development between patients who had received systemic antiviral treatment and those who had not [16].

Despite the aforementioned limitations, this study demonstrated a positive association between HZO and dementia. In patients with HZO, VZV vasculopathy may contribute to some degree to the pathogenesis of dementia. Therefore, clinicians must be alert to suspect dementia in patients with cognitive impairment who had prior HZO.

## References

1. Melesie G, Dinsa H. A literature review on: pathogenesis and management of dementia due to Alzheimer disease. *Bio-Genetics J* 2013;1: 18-31
2. O'Brien JT, Erkinjuntti T, Reisberg B, et al. Vascular cognitive impairment. *Lancet Neurol* 2003;2:89-98. 12849265
3. Chen JH, Lin KP, Chen YC. Risk factors for dementia. *J Formos Med Assoc* 2009;108:754-764. doi: 10.1016/S0929-6646(09)60402-2 19864195
4. Kalaria RN, Maestre GE, Arizaga R, et al. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. *Lancet Neurol* 2008;7:812-826. doi: 10.1016/S1474-4422(08)70169-8 18667359
5. Kivipelto M, Helkala EL, Laakso MP, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. *BMJ* 2001; 322: 1447-1451. 11408299
6. Gorelick PB. Risk factors for vascular dementia and Alzheimer disease. *Stroke* 2004; 35: 2620-2622. doi: 10.1161/01.STR.0000143318.70292.47 15375299
7. Newman AB, Fitzpatrick AL, Lopez O, et al. Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study cohort. *J Am Geriatr Soc* 2005;53:1101-1107. doi: 10.1111/j.1532-5415.2005.53360.x 16108925
8. Vagnucci AH, Li WW. Alzheimer's disease and angiogenesis. *Lancet* 2003; 361:605-608. doi: 10.1016/S0140-6736(03)12521-4 12598159
9. Wiesmann M, Kiliaan AJ, Claassen JA. Vascular aspects of cognitive impairment and dementia. *J Cereb Blood Flow Metab* 2013;33
10. Kleinschmidt-DeMasters BK, Gilden DH. The expanding spectrum of herpesvirus infections of the nervous system. *Brain Pathol* 2001;11:440-451. 11556690
11. Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. *Lancet Neurol* 2009;8:731-70. doi: 10.1016/S1474-4422(09)70134-6 19608099
12. Gilden DH, Lipton HL, Wolf JS, et al. Two patients with unusual forms of varicella-zoster virus vasculopathy. *N Engl J Med* 2002;347:1500-1503. doi: 10.1056/NEJMoa020841 12421892

13. Nagel MA, Gilden D. Update on varicella zoster virus vasculopathy. *Curr Infect Dis Rep* 2014;16:407. doi: 10.1007/s11908-014-0407-z 24819870
14. Bandeira F, Roizenblatt M, Levi GC Freitas DD, Belfort R Jr. Herpes zoster ophthalmicus and varicella zoster virus vasculopathy. *Arq Bras Oftalmol* 2016;79:126-129 doi: 10.5935/0004-2749.20160038 27224081
15. Kang JH, Ho JD, Chen YH, Lin HC. Increased risk of stroke after a herpes zoster attack: a population-based follow-up study. *Stroke* 2009;40:3443-3448. doi: 10.1161/STROKEAHA.109.562017 19815828
16. Lin HC, Chien CW, Ho JD. Herpes zoster ophthalmicus and the risk of stroke: a population-based follow-up study. *Neurology* 2010;74:792-797. doi: 10.1212/WNL.0b013e3181d31e5c 20200348
17. Schink T, Behr S, Thöne K, et al. Risk of Stroke after Herpes Zoster-Evidence from a German Self-Controlled Case-Series Study. *PLoS One* 2016;11:e0166554. doi: 10.1371/journal.pone.0166554 27880853
18. Tatemichi TK, Desmond DW, Mayeux R, et al. Dementia after stroke: baseline frequency, risks, and clinical features in a hospitalized cohort. *Neurology* 1992;42:1185-1193. 1603346
19. Moroney JT, Bagiella E, Desmond DW, et al. Risk factors for incident dementia after stroke. Role of hypoxic and ischemic disorders. *Stroke* 1996;27:1283-1289. 8711787
20. Corsari B, Manara O, Agostinis C, et al. Dementia after first stroke. *Stroke* 1996;27:1205-1210. 8685929
21. Liu HC, Lin KN, Teng EL, et al. Prevalence and subtypes of dementia in Taiwan: a community survey of 5297 individuals. *J Am Geriatr Soc* 1995;43:144-149. 7836638
22. Lin RT, Lai CL, Tai CT, et al. Prevalence and subtypes of dementia in southern Taiwan: impact of age, sex, education, and urbanization. *J Neurol Sci* 1998;160:67-75. 9804120
23. Fuh JL, Wang SJ. Dementia in Taiwan: past, present, and future. *Acta Neurol Taiwan* 2008;17:153-161. 18975520
24. López-Pousa S, Vilalta-Franch J, Llinàs-Regla J, et al. Incidence of dementia in a rural community in Spain: the Girona cohort study. *Neuroepidemiology* 2004;23:170-177. doi: 10.1159/000078502 15272219
25. Ravaglia G, Forti P, Maioli F, et al. Incidence and etiology of dementia in a large elderly Italian population. *Neurology* 2005;64:1525-1530. doi:

10.1212/01.WNL.0000160107.02316.BF 15883312

26. Ruitenberg A, Ott A, van Swieten JC, et al. Incidence of dementia: does gender make a difference? *Neurobiol Aging* 2001;22:575-580. 11445258

27. Appelros P, Stegmayr B, Terént A. Sex differences in stroke epidemiology: a systematic review. *Stroke* 2009;40:1082-1090. doi: 10.1161/STROKEAHA.108.540781 19211488

28. Petrea RE, Beiser AS, Seshadri S, et al. Gender differences in stroke incidence and poststroke disability in the Framingham heart study. *Stroke* 2009;40:1032-1037. doi: 10.1161/STROKEAHA.108.542894 19211484

29. Förster A, Gass A, Kern R, et al. Gender differences in acute ischemic stroke: etiology, stroke patterns and response to thrombolysis. *Stroke* 2009;40:2428-2432. doi: 10.1161/STROKEAHA.109.548750 19461021

30. Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Neurological disease produced by varicella zoster virus reactivation without rash. *Curr Top Microbiol Immunol* 2010;342:243-253. doi: 10.1007/82\_2009\_3 20186614

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**Editor:** Ilhem Messaoudi, University of California Riverside, UNITED STATES

Article History:

Received Date: 6/18/2017

Accepted Date: 11/5/2017

Published Date: 11/22/2017

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**Data Availability:** The LHID2005 is from the National Health Insurance Research Database (NHIRD), which has been transferred to the Health and Welfare Data Science Center (HWDC). Interested researchers can obtain the data through formal application to the HWDC, Department of Statistics, Ministry of Health and Welfare, Taiwan (<http://dep.mohw.gov.tw/DOS/np-2497-113.html>).

**Funding:** The author(s) received no specific funding for this work.

**Competing interests:** The authors have declared that no competing interests exist.

These authors contributed equally to this work: Chung-Chien Huang, Ben-Chang Shia, Li-Ting Kao, Heng-Ching Lin

DOI: 10.1371/journal.pone.0188490

**Source Citation** (MLA 8<sup>th</sup> Edition)

Tsai, Ming-Chieh, et al. "Increased risk of dementia following herpes zoster ophthalmicus." *PLoS ONE*, vol. 12, no. 11, 2017, p. e0188490. *Health Reference Center Academic*, [https://link.galegroup.com/apps/doc/A515331882/HRCA?u=cuny\\_york&sid=HRCA&xid=88cff0b4](https://link.galegroup.com/apps/doc/A515331882/HRCA?u=cuny_york&sid=HRCA&xid=88cff0b4). Accessed 14 May 2019.

**Gale Document Number:** GALE|A515331882