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Increased incidence of dementia following herpesvirus infection in the Korean population

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Abstract

Herpesviruses affect the development of dementia. We investigated the association between herpes infection and subsequent diagnoses of dementia. Data from the National Health Insurance Service of South Korea were used. Patients aged ≥50 years with the relevant diagnostic codes in the reference year 2009 were included and prospectively reviewed from January 2010 to December 2018. All study participants were followed from the index date until the onset of dementia, death, or the study endpoint. The three cohorts comprised 92,095 patients with herpes simplex virus (HSV) infections, 97,323 patients with varicella-zoster virus (VZV) infections, and 183,779 controls. During the follow-up period, 15,831 (17.19%) subjects with HSV infection and 17,082 (17.55%) VZV-infected subjects, compared to 27,028 (14.17%) control subjects, were subsequently diagnosed with dementia (all, $P < .001$). The adjusted hazard ratio for developing dementia was found to be 1.18 (95% confidence interval [CI]; 1.16–1.20) in HSV and 1.09 (95% CI; 1.07–1.11) in VZV patients (all, $P < .001$). HSV1 infections such as oral or ocular subtypes, but not HSV2, anogenital subtype, were associated with dementia, including several subtypes such as Alzheimer's disease (AD), vascular dementia, and dementia with Lewy bodies. VZV infection is also associated with AD. In this Korean nationwide population-based cohort study, both HSV and VZV infections were associated with a higher risk of dementia, particularly AD. Among the subtypes of HSV infection, HSV1 is associated with a risk of dementia. Further studies including appropriate public health interventions could evaluate the causality of these relationships.

Abbreviations: AD = Alzheimer's disease, Aβ = amyloid-beta, CI = confidence intervals, DLB = dementia with Lewy bodies, DM = diabetes mellitus, HR = hazard ratios, HSV1 = herpes simplex virus 1, HSV2 = herpes simplex virus 2, ICD-10 = International Classification of Diseases and Related Health Problems, 10th Revision, IDE = insulin-degrading enzyme, NHIS = National Health Insurance Service, VaD = vascular dementia, VZV = varicella-zoster virus.

Keywords: cohort studies, dementia, herpesvirus, population

1. Introduction

Dementia can develop from many different diseases, and its risk factors may be complex and heterogeneous. In Alzheimer's disease (AD), some pathological changes, besides those related to amyloid and tau pathologies, are considered to be related to dementia. The main risk factor is aging, but other defined risk factors include the allelic variant of apolipoprotein E ε4, low education level, traumatic head injury, and vascular factors such as hypertension, hyperlipidemia, stroke, and diabetes.[1–4] Additionally, several studies have proposed that infectious agents are associated with cognitive impairment and dementia.[5–7]

Several human herpesviruses with cutaneous manifestations are also common. The order Herpesvirales (family Herpesviridae) is characterized by latent and reactive phases of infection. The α-herpesvirinae subfamily consists of two genera, simplex virus (herpes simplex virus 1 [HSV1] and herpes simplex virus 2 [HSV2]) and varicellovirus (varicella-zoster virus [VZV]).[8] Members of this subfamily are especially neurotropic. These viruses are present in the brain and can induce amyloid-beta (Aβ) and AD-like tau, the hallmark pathological characteristics of AD.[9–11] This has led to the hypothesis that herpesvirus infection may underlie some causes of senile dementia. HSV infections have been reported to be related to AD,[9–11] and recurrent HSV1 infection can be considered a risk factor for AD.[7] Most of which harbors latent infections from several types of herpesviruses that were acquired during their lifetime. Infection rates are very low in neonates; however, in the case of HSV1, some 80% to 90% or more of the population is seropositive by the age of 70 years.[12] The virus is also present in the brain in many elderly people and AD patients, and sporadic reactivation of latent HSV1 in the brain, particularly in Apolipoprotein E4 carriers, was proposed to confer an increased risk of later developing AD.[13] The risk associations of dementia and another herpesvirus in the same group, VZV, have also been proposed several times. VZV causes chickenpox but remains in the body for life in its latent form after acute infection. It can reactivate later in life, causing shingles, referred to as herpes zoster.[14]

The authors have no conflicts of interest to disclose.

The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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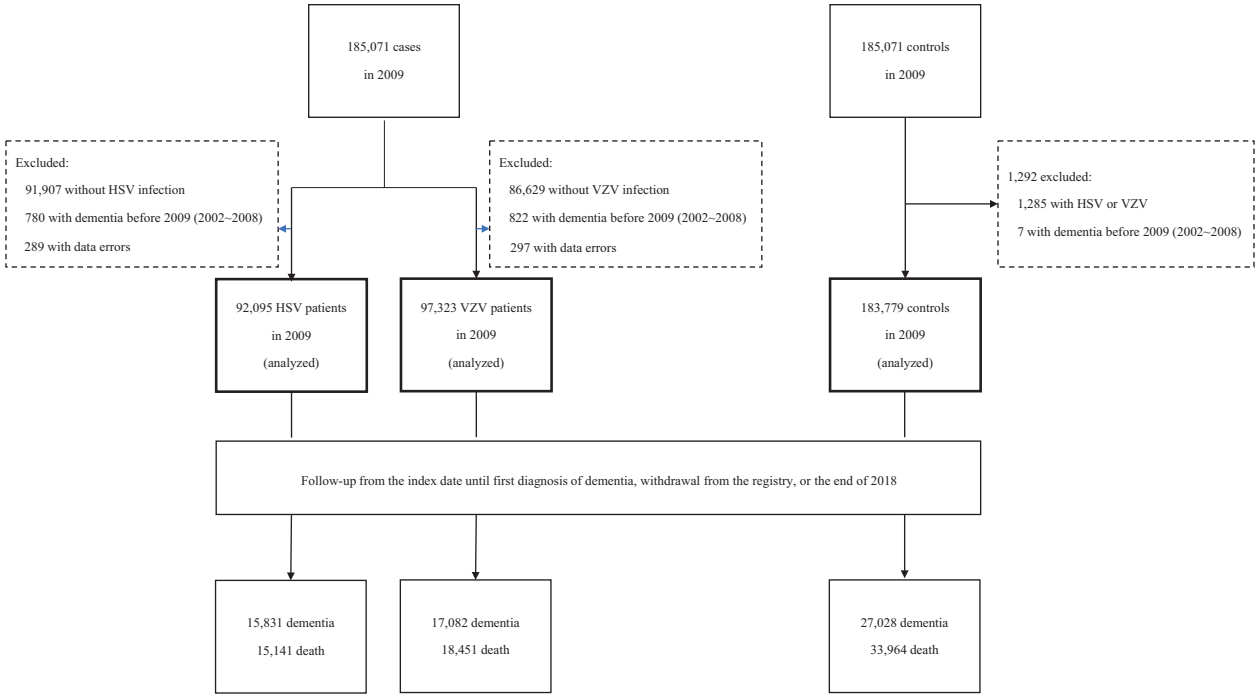


Figure 1. Flow chart of study population selection and matched analysis.

Herpesviruses may influence the development of dementia in terms of pathophysiology and etiology. Previous observational epidemiological studies have shown that herpesviruses may be associated with dementia. However, to overcome the limitations of previous studies that did not include the subtypes of both dementia and herpesvirus infections, the present study aimed to investigate whether various types of herpesviruses, including HSV1, HSV2, and VZV, are associated with the subsequent diagnosis of various types of dementia, taking advantage of a nationwide population-based cohort database.

2. Methods

2.1. Data sourcing and ethics

We used nationwide population-based cohort data from the National Health Insurance Service (NHIS) of South Korea. Approximately 97% of Korean residents are currently covered by health insurance based on employment or residential areas, and the rest are covered by a medical aid program (Medicaid). Information on patient demographic characteristics, medical records, and detailed diagnoses coded with the Korean Standard Classification of Diseases Version 8 (modification of the International Classification of Diseases and Related Health Problems, 10th Revision [ICD-10]) were collected from all individuals between January 2002 and December 2018. As the reference year of sampling was 2009, information from January 2002 to December 2008 was collected retrospectively, whereas information from January 2010 to December 2018 was collected prospectively.

2.2. Study design

A matched-cohort design was used in this study. From the NHIS, we identified 92,095 subjects diagnosed with HSV infections (B00* and A60*) and 97,323 subjects diagnosed with VZV infections (B02*) older than 50 years of age from January 1 to December 31, 2009, according to the ICD-10-Clinical Modification codes (Fig. 1). Each enrolled HSV and VZV patient was required to have made at least one inpatient or outpatient visit between January 1 and December 31, 2009, for symptomatic HSV or VZV infections according to their ICD-10-Clinical Modification codes. The date of diagnosis of HSV or VZV infection was defined as the index date. Additionally, HSV infections were subdivided into skin (B00, B00.1), oral (B00.2), ocular (B00.5†, H19.1*, H13.1*, H22.0*), anogenital (A60*: A60, A60.0, A60.01†, A60.04†, A60.1, A60.9), brain (B00.3†, B00.4†), unspecified (B00.9), and other manifestations (B00.7, B00.8). For each patient with HSV and VZV infections, we enrolled age- and sex-matched controls (n = 183,779) without a history of HSV or VZV infection. In the control group, patients diagnosed with dementia, HSV, or VZV infections before 2009 or before the first visit for HSV or VZV infections and all subjects aged <50 years were excluded.

2.3. Study outcomes

All study participants were followed from the index date until the onset of dementia, death, or the end of 2018. Participants with dementia were subdivided into AD (F00*, G30*), vascular dementia (VaD, F01*), frontotemporal dementia (G31.00, G31.01, G31.03, G31.04), dementia with Lewy bodies (DLB, G31.82, F02.8*), Parkinson's disease dementia (F02.3*), alcoholic dementia (F10.7), undetermined (F03*), and others (F02*: except F02.3*, G31.82 [F02.8*]). Individuals with codes for overlapping subtypes of dementia were counted as described above. Dementia was identified based on a diagnosis made during the follow-up period and the start of medical treatment, such as donepezil, galantamine, rivastigmine, and memantine, for at least 30 days for consistency and certainty.

Because we sought to define new cases of dementia, people who had received any dementia diagnosis according to medical claim data before the index date were excluded from the analysis.

2.4. Covariates

The covariates included age, sex, and comorbidities, including hypertension (I10), diabetes mellitus (DM, E10-14), dyslipidemia (E78: E78.0, E78.1, E78.4, E78.5), and previous stroke

Table 1

Baseline demographic characteristics of the study population and control group.

	Control group	*Herpesvirus group*	
	(n = 183,779)	HSV (n = 92,095)	VZV (n = 97,323)
Age (yr)	61.95 ± 9.68	62.51 ± 9.14	63.48 ± 9.37
Sex, male (%)	89900 (48.92%)	36074 (39.10%)	38193 (39.24%)
Comorbidities			
Hypertension	78275 (42.59%)	45749 (49.68%)	49781 (51.15%)
DM	47873 (26.05%)	30694 (33.33%)	33047 (33.96%)
Dyslipidemia	63019 (34.29%)	42678 (46.34%)	44622 (45.85%)
Previous stroke	10060 (5.47%)	6135 (6.66%)	7049 (7.24%)

Data are presented as mean ± standard deviation or number (%) unless otherwise indicated.
DM = diabetes mellitus, HSV = herpes simplex virus, VZV = varicella-zoster virus.

(I61-64; intracerebral hemorrhage [I61], other hemorrhage [I62], cerebral infarction [I63], and stroke, not specified as hemorrhage or infarction [I64]), based on the presence of diagnostic ICD-10 codes in medical claim data. All covariates were defined according to the above medical diagnoses from inpatient care data or on at least three occasions from outpatient care data during the entire study period.

2.5. Statistical analysis

Distributions between the HSV or VZV groups and control groups were described and compared using the χ^2 test for categorical variables and *t* tests for continuous variables. The incidence of dementia was analyzed and presented as the incidence rate per 1000 person-years. The cumulative difference in the risk of dementia between HSV- or VZV-infected subjects and the control group was estimated using the Kaplan–Meier method with the log-rank test. Multivariate Cox proportional hazards regression analysis was used to determine the risk of dementia, and the results are presented as hazard ratios (HR) with 95% confidence intervals (CI). The time-dependent Cox proportional hazards regression models were either unadjusted (Model 1) or adjusted for age, sex, and comorbidities (Model 2). To leave a latent period to observe whether the chronic progression of dementia occurred after the occurrence of HSV infection or herpes zoster and not beforehand,[15,16] we performed Cox proportional hazards regression analysis and calculated the Kaplan–Meier curve for those with >30 days between herpesviruses and dementia diagnoses. Statistical significance was defined as a two-tailed *P* value < .05. All data analyses were performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC). Restricted cubic splines in the Cox regression models were presented using the rms and spline packages in the R software version 3.3.3 (The R Foundation).

2.6. Ethics statement

This study was approved by the institutional review board of the Catholic University of Korea, Eunpyeong St. Mary's Hospital (PC19ZISI0111). Because the NHIS provided data after encryption to protect private information, the need for informed consent was waived.

3. Results

3.1. Subject characteristics

The three cohorts comprised 92,095 people with newly diagnosed HSV infections, 97,323 patients with VZV infections, and 183,779 matched control subjects. Table 1 shows the sex, age, and comorbidities of HSV- and VZV-infected patients and controls. Age, proportion of female participants, and comorbidities were higher in the two groups with herpesvirus infections than in the control group.

Subjects with HSV infections were subclassified according to the skin (n = 35,494, 38.54%), oral (n = 13,528, 14.69%), ocular (n = 11,756, 12.77%), anogenital (n = 2287, 2.48%), brain (n = 28, 0.03%), unspecified (n = 24,063, 26.13%), and other manifestations (n = 4939, 5.36%).

3.2. Association between herpes simplex virus and dementia

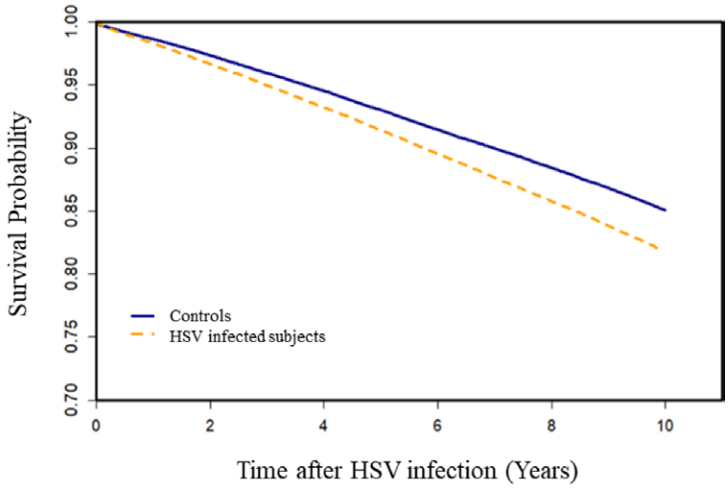
Of the 92,085 patients with HSV, 15,831 (17.19%) were diagnosed with dementia during the 10-year surveillance period, which was more frequent than that of the control group (n = 27,028, 14.17%) (*P* < .001). The mean ± standard deviation (SD) follow-up until the diagnosis of dementia was 4.92 ± 2.76 years for HSV patients and 5.15 ± 2.86 years for the controls (*P* < .001). The crude incidence rate covering 810,946 person-years with the HSV subjects was 19.74 (95% CI; 19.44–20.01) cases per 1000 person-years, which was higher than that of the control group, 16.03 (95% CI; 15.84–16.22), over 1,68,6173 person-years (*P* < .001]). The cumulative incidence of dementia between the HSV-infected subjects and control group was significantly different (log-rank test <0.001, Fig. 2).

Cox regression analysis showed that HSV infection was associated with the risk of developing dementia and various subtypes of dementia. After adjusting for covariates, the adjusted HR of HSV for dementia was 1.18 (95% CI; 1.16–1.20, *P* < .001). Covariates associated with the incidence of dementia were female sex, older age, and comorbidities such as hypertension, DM, hyperlipidemia, and previous stroke. HSV infections were also associated with an increased risk of subtypes of dementia, such as AD, VaD, and DLB, when compared to the control group (Table 2).

Among the various subtypes of HSV infections, the oral and ocular subtypes, but not the anogenital subtype, were associated with dementia (Table 3).

3.3. Association between herpes zoster virus and dementia

Of the 97,323 patients with VZV, 17,082 (17.55%) were diagnosed with dementia during the 10-year surveillance period, which was also different from that of the control group (*P* < .001). The mean follow-up period until the diagnosis of dementia was 4.86 ± 2.78 years for the VZV patients (*P* < .001). The crude incidence rate for dementia, covering 844,156 person-years, was 20.24 (95% CI; 19.93–20.54) cases per 1000 person-years in VZV subjects, which was higher than that of the control group (*P* < .001). The cumulative incidence of dementia between the VZV-infected subjects and the control group was also significantly different (log-rank test <0.001, Fig. 3).



Number at Risk

Controls	183779	178921	173749	168089	162518	0
Subjects with HSV infection	92095	89036	85867	82436	78985	0

Figure 2. Cumulative incidence of dementia after herpes simplex virus (HSV) infection. The Kaplan–Meier curve represents the cumulative incidence of dementia in the HSV group and the control group ($P < .001$ by the log-rank test).

Table 2

Risk of dementia and dementia subtypes after HSV and VZV infections.

	HSV		*VZV*	
	Adjusted HR (95% CI)	***P* value**	**Adjusted HR (95% CI)**	***P* value**
Dementia				
Unadjusted	1.25 (1.22~1.27)	<.001	1.28 (1.25~1.30)	<.001
Multivariate-adjusted	1.18 (1.16~1.20)	<.001	1.09 (1.07~1.11)	<.001
Dementia subtypes				
AD	1.121 (1.183~1.239)	<.001	1.106 (1.081~1.131)	<.001
VaD	1.069 (1.004~1.139)	.036	1.054 (0.992~1.120)	.090
DLB	1.398 (1.084~1.804)	.010	1.176 (0.908~1.524)	.220
PDD	0.706 (0.436~1.143)	.156	1.076 (0.722~1.605)	.718
FTD	1.778 (0.726~4.352)	.208	1.539 (0.631~3.751)	.343
Alcoholic	1.310 (0.718~2.390)	.379	0.877 (0.452~1.702)	.698
Others	1.193 (0.335~4.247)	.786	0.898 (0.223~3.605)	.879
Undetermined	1.142 (1.084~1.204)	<.001	1.101 (1.046~1.158)	<.001

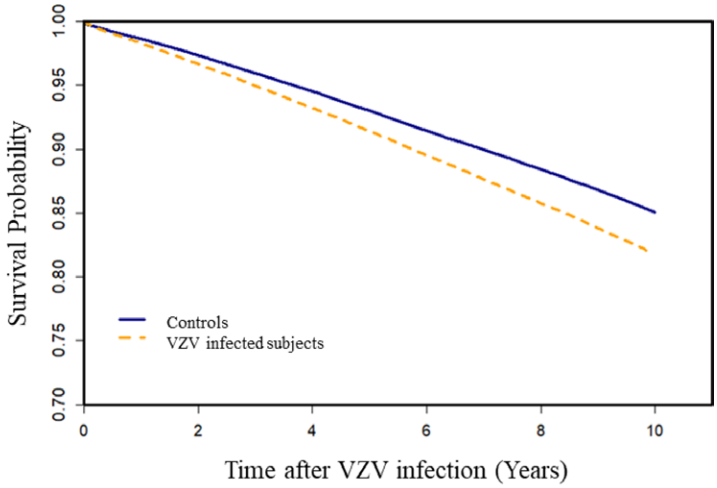
Unadjusted analysis was performed for the total cohort population. The results of the multivariate analysis are presented as adjusted hazard ratios. The following variables were adjusted for in the multivariate analysis: female sex, older age, and comorbidities such as hypertension, diabetes mellitus, hyperlipidemia, and previous stroke. Cox proportional hazards regression analysis was performed.
AD = Alzheimer's disease, CI = confidence interval, DLB = dementia with Lewy bodies, FTD = frontotemporal dementia, HR = hazard ratio, HSV = herpes simplex virus, PDD = Parkinson's disease dementia, VaD = vascular dementia, VZV = varicella-zoster virus.

Table 3

Risk of dementia after HSV infection according to the subtypes defined only by diagnostic code.

	Univariate			*Multivariate*		
	HR	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
HSV	1.25	1.22~1.27	<.001	1.18	1.16~1.20	<.001
Skin	0.99	0.96~1.02	.587			
Oral	1.50	1.45~1.56	<.001	1.27	1.23~1.32	<.001
Ocular	1.60	1.54~1.67	<.001	1.20	1.15~1.25	<.001
Anogenital	0.87	0.78~0.97	.013	1.08	0.97~1.21	.169
Brain	2.87	1.54~5.33	<.001	1.66	0.89~3.08	.110
Unspecified	1.06	1.02~1.10	<.001	1.08	1.05~1.12	<.001
Others	1.16	1.08~1.24	<.001	1.23	1.15~1..32	<.001

The results of multivariate analysis are presented as adjusted hazard ratios. The following variables were adjusted for in the multivariate analysis: female sex, older age, and comorbidities such as hypertension, diabetes mellitus, hyperlipidemia, and previous stroke. Cox proportional hazards regression analysis was performed.
CI = confidence interval, HR = hazard ratio, HSV = herpes simplex virus.



Number at Risk

Controls	183779	178921	173749	168089	162518	0
Subjects with VZV infection	97323	93899	90460	86850	83158	0

Figure 3. Cumulative incidence of dementia after varicella-zoster virus (VZV) infection. The Kaplan–Meier curve represents the cumulative incidence of dementia in the VZV group and the control group ($P < .001$ by the log-rank test).

The associations between HZV and dementia are summarized in Table 2. After adjusting for age, sex, and comorbidities, the adjusted HR was 1.09 (95% CI; 1.07–1.11, $P < .001$). VZV infections were associated with an increased risk of AD compared with those in the control group. Although univariate analysis showed associations between VZV, such as HSV, and VaD (HR 1.22; 95% CI 1.15–1.30, $P < .001$) and DLB (HR 1.34; 95% CI 1.04–1.73, $P = .026$), the statistical significance of these associations disappeared after adjusting for confounding factors.

4. Discussion

This Korean nationwide cohort study showed that 17.19% of patients with HSV and 14.17% of patients with VZV, aged ≥50 years in the reference year 2009, subsequently received a diagnosis of dementia during the 10-year follow-up period, and the risk of developing dementia in the HSV and VZV groups was found to be 1.18-fold and 1.09-fold greater, respectively, than that of the controls. Specifically, HSV1, such as the oral and ocular subtypes, and not the anogenital subtype, were associated with various subtypes of dementia, including AD, VaD, and DLB. VZV infection is also associated with AD.

We planned the present study to provide more confirmative, supportive results than the previous population studies.[17–19] In the present study, the diagnosis of dementia was defined by the diagnostic code with drug reimbursement data to include more refined cases. Vascular risk factors, such as hypertension, DM, dyslipidemia, and previous stroke, were controlled as covariates. Additionally, various subtypes of dementia and HSV infections were sub-classified according to their diagnostic codes. Meanwhile, two reports have been recently published since the previous studies from Taiwan.[17–19] Another population-based cohort study using the NHIS-National Sample Cohort in Korea showed that herpes zoster is associated with a higher risk of dementia, and the use of antiviral agents in patients with VZV infection was shown to decrease the risk of dementia.[20] This cohort randomly sampled approximately one million individuals, which is about 2% of the total Korean population. Although the effectiveness of antiviral therapy was not evaluated, the present study, using all available NHIS cohort data, showed similar results in that herpes zoster increased the risk of dementia. A multicenter observational cohort study using the health registry data from Wales, Germany, Scotland, and Denmark demonstrated contradictory findings with respect to antiviral drugs and dementia.[21] They showed heterogeneous results. In Denmark and Wales, short-term use of antiviral drugs slightly lowered the risk of dementia. Infected individuals in Germany who were not prescribed antiviral therapy had a slightly higher risk of dementia. Although there was a small but significant decrease in dementia incidence in those who had undergone antiherpetic administration, these results were not consistent across European countries. One possible explanation as to why the associations may not have been held in the European cohorts could be the treatment duration. In contrast to Korea and Taiwan, most Europeans took antiviral drugs for <30 days.[22] In addition, the complex nature of AD etiology and pathogenesis could result in inconsistent, heterogeneous results across cohorts. In contrast to data from Taiwan and Korea, which include health insurance claims information of nearly the entire national population, data from European cohorts did not represent the entire national population.

We might consider the possible mechanisms for the association between herpesviruses and dementia. Recent studies have also shown that viral infection itself may induce the formation of amyloid plaques, as HSV1 infection results in Aβ accumulation and tau phosphorylation in neuronal cells.[23,24] The insulin-degrading enzyme (IDE), which plays a major role in Alzheimer's disease by degrading Aβ, also functions as a cellular receptor of VZV.[25] Thus, it may be possible that the binding of VZV to IDE hinders the IDE-mediated degradation of Aβ, thereby leading to increased production of amyloid plaques.[26] Also, VZV may contribute directly to neuronal death and subsequent dementia by inducing local and systemic inflammation,[27] as VZV can transaxonally migrate to the central nervous system and induce subclinical inflammation.[28] As VZV and HSV1 both belong to the family Herpesviridae, VZV may also have similar effects on Aβ. VZV may also contribute to the development of dementia by inducing vasculopathy and subsequently increasing the risk of stroke, which in turn acts as a major risk factor for dementia.[29,30] Studies have also mentioned increases in dementia after a stroke, ranging from 3% to 19% in variable follow-up periods (from 3 months to 10 years).[31–33]

This study had several limitations. First, the present study, which is a retrospective cohort data study, cannot draw conclusions

regarding the causal relationship between dementia and HSV or VZV. Biases and confounders are major limitations of epidemiological studies. For example, in this nonrandomized, observational study, patients with herpesvirus infection, due to their acute symptoms, might be more prone to be neurologically assessed and have a better chance of early diagnosis of dementia. Furthermore, the data provided no information on the history of smoking, body mass index, education, or alcohol consumption, which may be risk factors and influence the pathogenesis of dementia as confounding factors.[34,35] Second, there is still some uncertainty in the diagnosis, as defined by the national health insurance claims data. However, we tried to reduce the inclusion of false diagnoses by including a history of cholinesterase inhibitor medication, and the reliability of the diagnostic code for VZV has been validated.[36,37] Finally, we did not compare the effect of antiviral treatment for VZV or HSV with a subsequent dementia diagnosis. Indeed, the association between antiviral therapy and the dramatic reduction in subsequent dementia incidence in patients with VZV has also been previously reported in Korea.[19,20] Phase II trials have been ongoing with valacyclovir, an anti-HSV drug, and apovir, a combination of two antiviral agents, pleconaril (active on enteroviruses) and ribavirin (active on several viruses).[38,39]

Despite these limitations, this study demonstrated a positive association between HSV and VZV infections, and dementia. Dementia should be suspected in patients with cognitive impairment who have herpesvirus infections. Moreover, the present study suggests appropriate public health interventions and warrants further studies on the causal relationship by investigating pathophysiological mechanisms and conducting interventional trials.

Author contributions

Conceptualization: YongSoo Shim.
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Investigation: YongSoo Shim, JaeYoung Kim.
Methodology: YongSoo Shim.
Writing – original draft: YongSoo Shim.
Writing – review & editing: YongSoo Shim.

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