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ORIGINAL ARTICLE

Symptomatic Herpes Simplex Virus Infection and Risk of Dementia in US Veterans: a Cohort Study

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Abstract

A Taiwanese cohort study found that symptomatic herpes simplex virus (HSV) infection was associated with a threefold increased risk of developing dementia; however, antiherpetic medication reduced the risk by 90%. Our aim was to verify and further investigate this finding in the US Veteran population using comprehensive electronic medical records from the Veterans Health Administration (VHA). Eighty-seven thousand six hundred eighty-seven Veterans aged 50 or older with symptomatic HSV-1/HSV-2 infection and 217,895 matched controls were identified in VHA data between January 1, 2001, and December 31, 2014, and followed until December 31, 2019. International Classification of Diseases (ICD) codes, ninth and tenth revisions, were used to define dementia. To define HSV infection, we utilized VHA data on antiherpetic medications and laboratory tests in addition to ICD codes. Cox proportional hazards models were used to analyze the effects of HSV infection and antiherpetic medication on the risk of developing dementia. The analysis revealed an adjusted HR of 0.80 (95% CI, 0.78–0.83) for the development of dementia among those with symptomatic HSV relative to those without. Among the 61,776 HSV-1/HSV-2 patients who were treated with antiherpetic medication, 4836 patients (7.8%) developed dementia (adjusted HR = 0.75; 95% CI, 0.72–0.78); this translated to a population average of one additional year of being dementia free in those who were taking antiherpetic medication. In contrast to Tzeng et al. we did not find that HSV infection was associated with an increased risk of dementia. Like their findings, we found that antiherpetic medication was associated with a protective effect against dementia. Future prospective studies are needed to further investigate this effect.

Keywords Dementia · Herpes simplex virus · Antiherpetic medications · Cohort study · Veterans

Introduction

Dementia is a clinical syndrome caused by damage to cerebral nerve cells and is characterized by a severe decline in mental ability that drastically reduces quality of life [1]. Alzheimer's disease (AD) and related dementias affect 1.6% of the United States (US) population, a figure projected to grow to 3.3% by 2060 [2]. The total global economic cost associated with dementia increased from $280 billion in 2000 to $948 billion in 2016, with the highest economic burden found in Europe and North America [3]. Epidemiological studies have identified several cardiovascular risk factors for dementia, such as age, diabetes mellitus, smoking, hypercholesterolemia, physical inactivity, increased fat intake, metabolic syndrome, and hypertension [4].

Previous studies have also reported evidence of considerable cerebrovascular pathology in AD. The toxic effects of vascular factors on the brain microvasculature may cause cerebral hypoperfusion and ischemia, resulting in impaired amyloid-β clearance as well as angiogenesis [5, 6]. Studies have recently indicated that herpes simplex virus (HSV) could be a major risk factor for AD [7–10]. In particular, Tzeng and colleagues [7] found that patients with symptomatic HSV infections had a three-fold increased risk of developing dementia compared to those without. Further, they found that the use of antiherpetic medications reduced the risk by almost 90% (adjusted HR = 0.09). However, they used insurance claims data which lacked laboratory confirmation and could not distinguish rule-out diagnosis events from true diagnoses.

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While these findings could improve our understanding of the etiology of dementia and signal new possible treatments, they first require confirmation in another population. We therefore conducted a similar analysis with US Veterans enrolled in the Veterans Health Administration (VHA) using comprehensive electronic medical records stored in the VHA Corporate Data Warehouse (CDW). Our aim was to verify and further investigate the association between herpes simplex virus infection and the risk of developing dementia, as well as the effect of antiherpetic medication on this risk.

Methods

Setting and Data Sources

The VHA is the largest integrated healthcare system in the US. It provides clinical care to more than 9 million military veterans at more than 1255 healthcare facilities, including 170 medical centers and 1074 outpatient sites [11]. VHA users can be followed across the care continuum, from the non-urgent outpatient clinic to the emergency department and subsequent hospitalization, to post-discharge extended care in rehabilitation and nursing facilities. Fifty percent of VHA enrollees are aged 65 years and older, and 90% are male [12].

Data for this study was extracted from the national clinical and administrative datasets of the VHA CDW, a healthcare encounters database that includes diagnoses, procedures, inpatient and outpatient pharmacy utilization, laboratory and radiology results, vital signs, and clinical notes. For research studies, CDW data is stored and analyzed within the Veterans Informatics and Computing Infrastructure (VINCI). Within VINCI, CDW data was linked to other patient-level data, including (1) demographic and mortality data from the VHA Enrollee Status File, which incorporates data from external sources including the Social Security Administration and Veterans Benefits Administration, and (2) claims data on VHA enrollees from Medicare fee-for-service files.

Study Design

We conducted a retrospective matched cohort study based on VHA patients selected from January 1, 2001, to December 31, 2014, and followed until December 31, 2019. This study period was chosen to allow for adequate follow-up time, as patients with newly diagnosed herpes simplex virus infections (HSV-1/HSV-2) could enter the study at any time within the 2001–2014 selection window. We had three cohort inclusion criteria: (1) continuous enrollment in VHA, (2) at least two health care encounters during the year prior to index date, and (3) at least 50 years of age at study entry (i.e., HSV-1/HSV-2 diagnosis date or matched date). To identify incident cases, we excluded patients with a diagnosis of dementia before or at the time of HSV diagnosis. We further excluded patients with a (1) positive cerebrospinal fluid polymerase chain reaction (PCR) laboratory result for HSV-1, as this would be evidence of HSV-1 encephalitis, which carries a very different prognosis with regards to cognitive status; (2) negative HSV laboratory result and a varicella zoster virus (VZV) diagnosis with a prescription for acyclovir or valacyclovir intended for VZV; (3) negative HSV laboratory result and a cytomegalovirus (CMV) diagnosis with a prescription for ganciclovir or valganciclovir intended for CMV.

Baseline Characteristics

Characteristics measured during the baseline period (i.e., 1 year prior to study entry) included demographics, comorbidities, and healthcare utilization. Demographics included age, sex, race, rurality, and priority rating for VHA care as a proxy for socioeconomic status [13].

Symptomatic Herpes Simplex Virus Infections

The main exposure of our study was symptomatic HSV-1/HSV-2 infection (hereinafter simply referred to as HSV). This was defined according to a mixed criteria of diagnosis codes, antiherpetic prescription history, and laboratory results: *either* (1) a positive HSV laboratory result, (2) an outpatient diagnosis combined with an HSV antiviral regimen, *or* (3) an HSV laboratory result (negative or positive) combined with an HSV antiviral regimen. For diagnoses, we used a crosswalk of ICD 9th and 10th revision codes. The index date was defined as the earliest date of HSV diagnosis, treatment, or laboratory result, whichever occurred first.

Dementia

Dementia was defined using ICD-9 and ICD-10 codes (Appendix). Incidents of dementia and associated dates were subsequently identified using inpatient and outpatient medical records.

Antiherpetic Medication Usage

For both case identification and follow-up exposure, we defined antiherpetic medication usage using the same list of oral medications as Tzeng et al.: acyclovir, famciclovir, ganciclovir, valacyclovir, and valganciclovir. For follow-up exposure, we calculated the total days of supply among all antiherpetic prescription fills during the follow-up period for each subject. For some, antiherpetic medication could start later than the index date and thus create a period of

"immortal" time for the analysis of antiherpetic medication (i.e., a period where a subject could not have an outcome or be censored). To address this immortal time bias, for all antiherpetic medication analyses, we adjusted the index date for those using antiherpetic medication to be the date of their first antiherpetic medication prescription after their entry into the study.

Potential Confounders

We identified several risk factors for dementia as potential confounders. These included age, rurality, socioeconomic factors (e.g., VHA priority rating), and diagnoses. Diagnoses included ischemic stroke, autoimmune disease (or immunosuppressant use), and alcohol use disorder (Table 1). Comorbidities were defined according to an adaptation of the Deyo-Charlson comorbidity score [14] using diagnosis codes captured during inpatient and outpatient visits. As a proxy measure for frailty, we used the Care Assessment Needs (CAN) score. The CAN score was developed specifically to predict hospitalization within 1 year among VHA patients. In addition to incorporating the medical conditions used in the Charlson and Elixhauser scores [15], the CAN score captures sociodemographic characteristics, recent levels of healthcare utilization, medication use, and results of laboratory tests [16]. Finally, we included comorbidities more prevalent among Veterans such as traumatic brain injury (TBI), depression, and posttraumatic stress disorder (PTSD), as all have been associated with increased risk of dementia [17, 18].

Ethics Statement

This study was approved by the Veteran's Institutional Review Board of Northern New England at the White River Junction VHA Medical Center (No. 903343). All study procedures were carried out in compliance with federal and institutional ethical guidelines. The requirement to obtain informed consent from study participants was waived as there was no more than a minimal risk to the privacy of individuals.

Statistical Analysis

Each patient with symptomatic HSV infection was matched with up to three controls without evidence of HSV infection on exact age, sex, race, rurality, VHA priority rating, medical facility, and having at least one outpatient visit to a VHA facility during the same month and year as the index date of the corresponding HSV patient (of these dates, the closest was used to define the control index date). We used standardized mean difference (SMD) as a measure of statistical difference between subjects and controls, with a value greater than 10 denoting statistical significance [19].

As conducted by Tzeng and colleagues in their main analyses, we used matched Cox proportional hazards modeling to estimate the hazard ratios (HR) and 95% confidence intervals (CIs) for the association between symptomatic HSV infection and dementia risk during follow-up. Follow-up time started at the index date and ended on the date of the earliest diagnosis of dementia, death, or the end of the study period (December 31, 2019), whichever occurred first. The same model was also used to explore the association between total length of antiherpetic medication coverage and dementia risk.

Because of the risk that antiherpetic medication supply, age, and length of follow-up are intertwined, we conducted several sensitivity analyses to rule out spurious associations between antiherpetic medication and subsequent dementia.

First, we constructed Cox survival models stratified by age group and length of antiherpetic treatment. We then adjusted these models for length of follow-up and interaction with length of treatment. Second, there is the possibility that patients without a dementia diagnosis would accrue antiherpetic medication exposure until the end of follow-up, while patients with a diagnosis of dementia would accrue antiherpetic medication exposure only until the date of dementia diagnosis and be censored afterward. To account for this, we conducted a nested case–control study, where cases are those who developed dementia, and controls are those who did not develop dementia. We matched cases to controls on length of follow-up and ensured that controls had a VHA healthcare encounter during the same month and year as the dementia diagnosis of their corresponding case. Because this nested study followed a case–control design, we applied conditional logistic regression to examine the association between days of supply and subsequent dementia.

Finally, to account for the possibility of dementia diagnoses outside of the VHA system, we restricted our study population to those enrolled in both VHA and Medicare and repeated our main analysis using both CMS and VHA dementia diagnoses. For this analysis, we also included potential confounders that were not balanced after our matching strategy. Because the impact of antiherpetic medication on the risk of dementia, if real, could lead to potential pharmacological intervention for the prevention of dementia, we wanted to further quantify this impact in a more interpretable way. Instead of presenting hazard ratios in this final sensitivity analysis, we estimated additional dementia-free years. Estimation was performed using inverse-probability treatment weighting (IPTW) [20]. IPTW estimators use weighted averages of the observed outcome. The estimated weights correct for missing data on the potential outcomes and for censored survival times.

Table 1 Baseline characteristics of matched HSV and control cohorts

	HSV subjects ($n=87,687$)	Controls ($n=217,895$)	SMD
Sex			
Female	5794 (6.6%)	11,863 (5.4%)	4.9
Male	81,893 (93.4%)	206,032 (94.6%)	4.9
Race			
(Missing)	2944 (3.4%)	7438 (3.4%)	0.3
Black	16,513 (18.8%)	40,623 (18.6%)	0.5
Other	3988 (4.5%)	8571 (3.9%)	3.0
White	64,242 (73.3%)	161,263 (74.0%)	1.7
Age			
50–59	37,693 (43.0%)	92,043 (42.2%)	1.5
60–69	32,152 (36.7%)	81,170 (37.3%)	1.2
70–79	12,911 (14.7%)	32,838 (15.1%)	1.0
80+	4931 (5.6%)	11,844 (5.4%)	0.8
Rurality			
(Missing)	133 (0.2%)	305 (0.1%)	0.3
Rural and highly rural	28,196 (32.2%)	79,047 (36.3%)	8.7
Urban	59,358 (67.7%)	138,543 (63.6%)	8.7
Priority			
(Missing)	16 (0.0%)	39 (0.0%)	0.0
Level 1	11,694 (13.3%)	27,793 (12.8%)	1.7
Level 2	5309 (6.1%)	13,128 (6.0%)	0.1
Level 3	9981 (11.4%)	25,139 (11.5%)	0.5
Level 4	242 (0.3%)	484 (0.2%)	1.1
Level 5	23,983 (27.4%)	59,044 (27.1%)	0.6
Level 6	5317 (6.1%)	13,347 (6.1%)	0.3
Level 7	7066 (8.1%)	17,694 (8.1%)	0.2
Level 8	24,079 (27.5%)	61,227 (28.1%)	1.4
Comorbidities			
PTSD	10,907 (12.4%)	25,465 (11.7%)	2.3
TBI	108 (0.1%)	323 (0.1%)	0.7
Ischemic stroke	1628 (1.9%)	5856 (2.7%)	5.6
Stroke TIA	2255 (2.6%)	7460 (3.4%)	5.0
Diabetes	18,497 (21.1%)	60,118 (27.6%)	15.2
Addiction disorder	14,495 (16.5%)	43,358 (19.9%)	8.7
Anxiety	7873 (9.0%)	17,391 (8.0%)	3.6
Depressive disorder	15,349 (17.5%)	36,198 (16.6%)	2.4
CHF	3213 (3.7%)	11,027 (5.1%)	6.8
Schizophrenia	1738 (2.0%)	7848 (3.6%)	9.8
COPD	7295 (8.3%)	22,389 (10.3%)	6.7
Autoimmune disease	1460 (1.7%)	2975 (1.4%)	2.5
Alcohol use disorder	4276 (4.9%)	13,247 (6.1%)	5.3
Care assessment needs score—average 1-year probability			
Mortality	3%	3%	6.5
Hospitalization	16%	14%	11.0
Any visit	17%	15%	9.2

All tests were two-tailed, and 0.05 was the chosen level of statistical significance. All statistical analyses were performed using Stata 15 (StataCorp, College Station, TX).

Results

A total of 87,687 subjects with symptomatic HSV met inclusion criteria. These subjects were matched to 217,895 controls with no evidence of symptomatic HSV in baseline or follow-up periods (Table 1). HSV patients and their controls were well matched, with SMDs below our threshold for significance on most of the matching variables (Table 1). For the few variables that matching did not balance, we included them in our IPTW model.

HSV subjects were followed for a median of 8.9 years (IQR, 6.0–12.2), and 6,925 (7.9%) developed dementia (Table 2). Controls were followed for a median of 8.0 years (IQR, 5.2–11.3), and 17,680 (8.1%) developed dementia. Patients with HSV had a 20% lower risk of developing dementia compared to their matched controls (HR = 0.80; 95% CI, 0.78–0.83). This association can be broken out into two parts. First, among the 25,911 HSV patients who were not treated with antiherpetic medication, 2089 patients (8.1%) developed dementia (adjusted HR = 0.94; 95% CI, 0.88–0.99; compared to their matched controls). In contrast, among the 61,776 HSV patients who were treated with antiherpetic medication, 4836 patients (7.8%) developed dementia (adjusted HR = 0.75; 95% CI, 0.72–0.78; compared to their matched controls). This protective association was also seen in our IPTW-adjusted model (additional dementia-free years = 1.15; 95% CI, 1.05–1.26).

Among those with HSV, 70.5% (n = 61,776) were treated with antiherpetic medication over a median follow-up of 9.5 years (IQR, 6.4–12.9). Table 2 shows that among those with HSV, any antiherpetic medication coverage was associated with a 25% decreased risk of dementia (HR = 0.75; 95% CI, 0.72–0.78; compared to their matched controls). Furthermore, longer durations of coverage were associated with greater reductions in risk. For example, those with greater than one year of antiherpetic coverage had a 43% decreased risk of dementia (HR = 0.57; 95% CI, 0.53–0.61); this translates to a population average of an additional 1.67 dementia-free years (Table 2).

In our first sensitivity analysis (Table 3), we found similar results for the protective effect of antiherpetic coverage among all age strata; as the length of treatment increased, the

Table 2 Risk of dementia among HSV and control cohorts

	Matched controls	Matched HSV cohorts			Subgroups of antiherpetic medication cohort by length of treatment			
	Non-HSV cohort	Total HSV cohort	No antiherpetic medication	Antiherpetic medication	1–29 days	30–179 days	180 days–1 year	Longer than 1 year
No. of subjects	217,895	87,687	25,911	61,776	21,656	16,049	6218	17,853
No. of dementia cases	17,680	6925	2089	4836	2065	1180	411	1180
Median length (years) of follow-up (IQR)	8.0 (5.2–11.3)	8.9 (6.0–12.2)	7.7 (5.2–10.5)	9.5 (6.4–12.9)	8.7 (5.8–12.1)	9.1 (6.2–12.6)	9.6 (6.4–13.1)	10.6 (7.4–14.0)
Cumulative incidence rate (%)	8.1%	7.9%	8.1%	7.8%	9.5%	7.4%	6.6%	6.6%
IPTW: dementia-free years (95% CI)	Reference	0.91 (0.81, 1.01)	0.35 (0.20, 0.51)	1.15 (1.05, 1.26)	0.79 (0.64, 0.95)	1.14 (0.96, 1.32)	1.07 (0.78, 1.37)	1.67 (1.51, 1.84)
HR (95% CI)	Reference	0.80 (0.78, 0.83)	0.94 (0.88, 0.99)	0.75 (0.72, 0.78)	0.93 (0.87, 0.98)	0.75 (0.70, 0.81)	0.72 (0.63, 0.81)	0.57 (0.53, 0.61)
Tzeng HR (95% CI)[a]	Reference	0.74 (0.72, 0.77)	1.04 (0.91, 1.19)	0.73 (0.70, 0.75)	0.90 (0.85, 0.96)	0.72 (0.67, 0.78)	0.71 (0.62, 0.81)	0.55 (0.51, 0.60)

[a]Tzeng HR (95% CI) uses the same dementia and HSV ICD codes and requires at least 3 encounters for HSV during the enrollment year as done by Tzeng et al

Table 3 Risk of dementia by antiherpetic medication use and age

	Total	Age 50–59	Age 60–69	Age 70–79	Age 80 +
No. of subjects	305,582	129,204	113,619	45,876	16,883
No. of dementia cases	24,605	5829	8241	7106	3429
Median length (years) of follow-up (IQR)	8.3 (5.4–11.6)	9.5 (6.4–13.0)	8.1 (5.5–10.9)	6.8 (3.8–10.2)	4.7 (2.2–7.4)
Cumulative incidence rate (%)	8.1%	4.5%	7.3%	15.5%	20.3%
Matched Cox regression HR (95% CI)					
1–29 days	0.82 (0.77, 0.87)	0.78 (0.68, 0.89)	0.91 (0.82, 1.01)	0.79 (0.71, 0.89)	0.73 (0.62, 0.86)
30–179 days	0.78 (0.72, 0.84)	0.84 (0.72, 0.99)	0.81 (0.71, 0.94)	0.67 (0.57, 0.79)	0.77 (0.60, 0.98)
180 days–1 year	0.72 (0.64, 0.80)	0.74 (0.61, 0.91)	0.74 (0.62, 0.88)	0.76 (0.62, 0.93)	0.48 (0.33, 0.70)
Longer than 1 year	0.61 (0.58, 0.64)	0.58 (0.53, 0.64)	0.62 (0.57, 0.67)	0.64 (0.58, 0.71)	0.59 (0.49, 0.71)
Matched Cox regression (95% CI) with length of follow-up and interaction with length of treatment					
1–29 days	0.97 (0.81, 1.15)	1.30 (0.70, 2.40)	1.00 (0.64, 1.55)	0.87 (0.65, 1.16)	0.99 (0.75, 1.31)
30–179 days	0.64 (0.49, 0.82)	0.84 (0.35, 2.02)	0.54 (0.27, 1.06)	0.57 (0.38, 0.86)	0.71 (0.47, 1.08)
180 days–1 year	0.73 (0.46, 1.14)	1.16 (0.24, 5.69)	0.38 (0.13, 1.06)	1.01 (0.49, 2.10)	0.65 (0.28, 1.49)
Longer than 1 year	0.42 (0.30, 0.59)	0.81 (0.23, 2.77)	0.42 (0.18, 0.95)	0.32 (0.17, 0.59)	0.45 (0.27, 0.75)

Rows 1–4 refer to the total study population. Hazard ratios show antiherpetic medication cohort relative to non-HSV cohort

associated risk for developing dementia decreased regardless of age at diagnosis. However, when we introduced length of follow-up into the survival model and its interaction term with length of treatment, the protective effect disappeared for some strata. For example, among those who entered the study in their 70 s and were prescribed antiherpetic medication for 6 months to 1 year, the protective effect disappeared (HR = 1.01; 95% CI, 0.49–2.10). However, we continued to observe an overall protective effect for antiherpetic medication coverage.

In our second sensitivity analysis (Table 4), the nested case–control study, HSV infection was again associated with a protective effect against dementia (OR = 0.83; 95% CI, 0.80–0.88). Antiherpetic coverage was also associated with a protective effect against dementia (OR = 0.88; 95% CI, 0.83–0.93). However, we failed to observe a consistent dose–response despite having a sample size equal to the entire study population in Tzeng et al.

In our third sensitivity analysis, we repeated our main analysis on the Medicare-enrolled subset of our matched cohorts, using CMS dementia diagnoses to supplement those from VHA. We also included variables that were unevenly distributed between the matched cohorts (e.g., diabetes, Table 1). To better control for the confounding effects of age and length of follow-up on antiherpetic medication use, we conducted IPTW and estimated dementia-free years. We present these dementia free years alongside our main analysis in Table 2 to provide a concrete interpretation of the hazard ratios. Length of follow-up was adjusted here, but again did not present a consistent dose–response. For days of supply 1–29 days, 30–179 days, 180 days–1 year, and longer than 1 year, we found dementia-free years to be 0.79 (95% CI, 0.64–0.95), 1.14 (95% CI, 0.96–1.32), 1.07 (95% CI, 0.78–1.37), and 1.67 (95% CI, 1.51–1.84) respectively. Overall, the 25% protective effect that we gleaned from an HR of 0.75 (95% CI, 0.72–0.78) translates to a population average of roughly 1 additional dementia-free years (1.15; 95% CI, 1.05–1.26) (Table 2).

Discussion

Neuroinflammation is present in Alzheimer's disease, but it is unclear whether it is a cause or a consequence of neurodegeneration. It has been suggested that neurotropic microorganisms, "particularly those capable of producing ineradicable infection, like herpesvirus, theoretically could trigger chronic neuroinflammation" [21]. In this study, we focused

Table 4 Risk of dementia using nested case–control design

HSV OR (95% CI)			With antiherpetic medication use OR (95% CI)			
Total	No antiherpetic medication	Antiherpetic medication	1–29 days	30–179 days	180 days–1 year	Longer than 1 year
0.83 (0.80–0.88)	0.79 (0.73–0.85)	0.88 (0.83–0.93)	0.92 (0.86–0.99)	0.90 (0.82–0.98)	0.81 (0.72–0.90)	0.83 (0.78–0.88)

Cases are study subjects who developed dementia, and controls are study subjects who did not

on exploring the potential link between herpes simplex virus infection and dementia epidemiologically. Previous findings based on claims data were intriguing [7], resulting in calls for replication studies [21]. In our study, symptomatic HSV patients and their matched controls shared a similar risk of developing dementia. Survival analyses revealed that untreated HSV patients and their controls had the same 10-year dementia-free survival rate, 97%. And their cumulative incidence rates were almost identical as well, 7.9% (HSV) vs. 8.1% (controls). These rates are reflected in other studies of dementia among Veterans. Yaffe et al. [17] reported a cumulative incidence rate of 6.6% for a cohort of 127,938 Veterans without PTSD, with a starting age of 55, mean age of 70, and an average 7-year follow-up. In our study, the median length of follow-up was 8.9 years (IQR, 6.0–12.2) for symptomatic HSV patients and 8 years (IQR, 5.2–11.3) for controls. Even when patients with a diagnosis of dementia within the first year and the first 5 years were excluded, HSV infection was still associated with a lower risk of dementia.

By comparing hazard ratios, we see that antiherpetic medication contributed overwhelmingly to the overall protective effect associated with HSV (HR = 0.80; 95% CI, 0.78–0.83), since the HR was only 0.94 (95% CI, 0.88–0.99) among those who were *not* treated with antiherpetic medication. Among patients with symptomatic HSV who *were* treated with antiherpetic medication, we found a substantially lower risk of developing dementia relative to non-HSV controls, with an adjusted HR of 0.75 (95% CI, 0.72–0.78). This was further validated by the case–control sensitivity analysis, where we found an OR of 0.88 (95% CI, 0.83–0.93). Using total days of supply as an indicator for the cumulative exposure to antiherpetic medication, we found a dose–response effect in our survival models that, although tantalizing, was clearly confounded by length of follow-up. After adjusting for length of follow-up, the dose–response effect became inconsistent (Table 2 (IPTW portion), Table 3, and Table 4); nevertheless, the protective effect remained.

Beyond the known antiviral activity, there is no published data to suggest that antiherpetic medications could reduce overall inflammation. As an ad hoc analysis (results not shown), we examined the C-reactive protein levels (CRP) and erythrocyte sedimentation rates (ESR) of our study population and found that those who received antiherpetic prescriptions had reduced levels of CRP and ESR; there was also a dose–response associated with longer lengths of medication use. Acyclovir and Valacyclovir, two of the most frequently prescribed antiherpetic medications, are activated by viral thymidine kinase and inhibit viral DNA polymerase which blocks viral DNA synthesis [22]. By blocking DNA synthesis, they can stop viral replication and decrease viral shedding. The decreased burden of viral load may be reflected in overall decreases in CRP and ESR. Although previously this has only been observed among those with active herpesvirus infections, those who take antiherpetic medication prophylactically to prevent herpes infection flare-ups may be achieving lower CRP and ESR through suppression of viral replication in the peripheral nervous system. The anti-inflammatory property of HSV antivirals deserves to be carefully examined in future studies.

As a verification study, this study closely followed the statistical methods of Tzeng and colleagues—Cox proportional hazard models on matched cohorts. However, since our matching strategy resulted in balanced distributions for most medical conditions between those with and without HSV (Table 1), we did not explicitly adjust for medical conditions other than diabetes in our main analysis. Instead, additional confounders were all adjusted in our IPTW analysis. To account for the possibility that different dementia definitions drove the differences in findings between our study and Tzeng et al. we conducted a sensitivity analysis using strictly the dementia diagnosis codes used by Tzeng et al. However, the results did not differ substantially from our own (Table 2).

Much background work was conducted before the main analyses to guide our focus. We concentrated on HSV as one exposure because stratified analyses by HSV and dementia-type did not show meaningful differences between groups, demonstrated by similar magnitudes of relative risk and overlapping confidence intervals (Table 5). The types of HSV laboratory tests available at the VA and their usage informed the criteria we used to define symptomatic HSV (Table 5).

Limitations

HSV is highly prevalent in North America; in the 50 + age group described in this study, it could be in the 80 to 90% range [23]. As a result, our controls likely have some incidence of HSV infection that was not captured in our data, which is why our study focused on symptomatic HSV cases (i.e., those with evidence of HSV in health records). This might have contributed to our failure to find an increased risk of developing dementia among symptomatic HSV patients, as the high level of population prevalence likely made the controls a group of asymptomatic HSV subjects rather than a group without HSV at all. We plan to carry out a separate study of VZV, as Tzeng et al. did not include it in their study for HSV.

To limit the number of false positives in our HSV cohorts, our definition of HSV ensured that (1) those with antiherpetic treatment also had either an HSV diagnosis or a laboratory test for HSV (positive or negative), and (2) those without treatment had a positive laboratory test for HSV. But some patients could have obtained HSV-related medical care from outside the VA or outside our study period, and the

Table 5 Dementia risk by HSV and dementia type

	All dementia	Vascular	Alzheimer's	Others
HR: Cox proportional hazard model (95% CI)				
HSV1	0.78 (0.75–0.81)	0.75 (0.69–0.82)	0.83 (0.76–0.91)	0.87 (0.83–0.92)
HSV2	0.79 (0.75–0.84)	0.80 (0.70–0.90)	0.92 (0.79–1.09)	0.85 (0.78–0.92)
HSV1/2	0.80 (0.78, 0.83)	0.78 (0.73–0.84)	0.88 (0.82–0.94)	0.88 (0.85–0.92)
IPTW: Dementia-free years (95% CI)				
HSV1	0.85 (0.76–0.94)	0.53 (0.28–0.79)	0.67 (0.40–0.95)	0.40 (0.26–0.54)
HSV2	0.92 (0.81–1.03)	0.43 (0.08–0.78)	0.66 (0.30–1.02)	0.50 (0.31–0.70)
HSV1/2	0.91 (0.81–1.01)	0.50 (0.30–0.71)	0.68 (0.46–0.90)	0.43 (0.32–0.54)
Patient distribution by HSV diagnosis codes				
HSV1	054.xx other than 054.1	65%		
HSV2	054.1	24%		
HSV1/2	054.xx	11%		
Patient distribution by elements of symptomatic HSV				
LAB (+) only	RX + LAB (+/−) only	DX + LAB (+) only	DX + RX only	DX + RX + LAB (+/−)
25%	4%	5%	62%	4%
Distribution of HSV laboratory tests by type				
Serology	PCR	Culture	Antigen	Unknown
87%	8%	2%	1%	2%

resulting misclassifications (i.e., classifying HSV patients as non-HSV, and classifying treated patients as untreated) may have biased our results toward the null. Untreated and treated HSV patients are clearly different so our comparisons were consistently made to their matched controls and not between each other.

Our study population consisted of primarily male veterans, which means the results may not be generalizable to females or to the non-Veteran population. Likewise, it would be challenging to compare this study to seroprevalence studies in Europe and North America, in which far more females than males are reported to have either HSV-1 or HSV-2 infections [24]. We used days of supply as a measure of cumulative exposure to antiherpetic medication, a proxy measure which does not perfectly capture adherence. We did not use cognitive assessment or imaging findings to confirm dementia diagnosis. Finally, while we carefully controlled for potential confounders available in the data, there may be residual confounding factors, such as genetics, physical activity, education, or dietary factors, which we were unable to control for.

Conclusion

In contrast to Tzeng et al. we did not find that HSV infection was associated with an increased risk of dementia. Like their findings, we found that HSV patients who received antiherpetic medications had a significantly lower rate of dementia when compared to a matched control population. We observed a dose–response relationship between length of supply and reduced risk of dementia, further supporting a protective role for antiherpetic medications. However, this relationship could be partially confounded by length of follow-up, as suggested by our sensitivity analysis.

In summary, incidence rates and survival functions showed no significant differences among the three groups—those without symptomatic HSV, those with HSV but no record of antiherpetic medication, and those with both HSV and a record of antiherpetic medication. However, the possible protective effect of antiherpetic medication deserves further investigation.

Appendix

Diagnosis codes for dementia

Primary dementia ICD codes			Other dementia-related ICD codes		
Dementia type	ICD-9/10	(Tzeng et al.) [7]	ICD-9	(Tzeng et al.) [7]	ICD-10
Alzheimer's	331.0	331.0	290.10	290.10	F01.51
Alzheimer's	G30.9		290.11	290.11, 290.12	F02.80

Primary dementia ICD codes			Other dementia-related ICD codes		
Dementia type	ICD-9/10	(Tzeng et al.) [7]	ICD-9	(Tzeng et al.) [7]	ICD-10
Frontotemporal	331.1		290.13	290.13	F02.81
Frontotemporal	G31.09		4290.21	290.21	F03.91
Lewy body	331.82		290.8	290.8	F10.27
Lewy body	G31.83		290.9	290.9	F10.97
Unspecified	294.8		291.1		F13.27
Unspecified	F06.0		291.2		F13.97
Unspecified	F06.8		292.82		F18.17
Senile	290.0	290.0	294.10		F18.27
Senile	290.2	290.20, 290.21	294.11		F18.97
Senile	290.3	290.3	294.2		F19.17
Senile	331.2		294.21		F19.27
Senile	F03.90		304.10		F19.97
Senile	F05		304.60		G30.0
Senile	G31.1				G30.1
Vascular	290.4	290.41–290.43			G30.8
Vascular	F01.50				G31.01

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