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Association between herpes simplex virus type 1 and the risk of Alzheimer's disease: a retrospective case–control study

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ABSTRACT

Objective A growing body of evidence points to a role for herpesviruses in the development of Alzheimer's disease (AD) and a reduced risk of AD among patients receiving antiherpetic medications. We investigated the association between herpes simplex virus type 1 (HSV-1) and AD using real-world data (RWD) from USA.

Design In a matched case–control study, patients with AD aged ≥50 years diagnosed between 2006 and 2021 were identified from the IQVIA PharMetrics Plus claims database. Controls were matched in a 1:1 ratio with subjects with AD on age, sex, region, database entry year and healthcare visit numbers.

Results The study included 344 628 AD case–control pairs. History of HSV-1 diagnosis was present in 1507 (0.44%) patients with AD compared with 823 (0.24%) controls. HSV-1 diagnosis was found to be associated with AD (adjusted OR 1.80; 95% CI 1.65 to 1.96). Patients with HSV-1 who used antiherpetics were less likely to develop AD compared with those who did not use antiherpetics (adjusted HR 0.83, 95% CI 0.74 to 0.92).

Conclusions Findings from this large RWD study implicate HSV-1 in the development of AD and highlight antiherpetic therapies as potentially protective for AD and related dementia.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A matched case–control study was conducted using large administrative claims data from the USA.
⇒ This study highlights the clinical value of HSV-1 infection in the pathogenesis of Alzheimer's disease.
⇒ Asymptomatic HSV-1 infection is difficult to capture in a real-world setting.

BACKGROUND

There are approximately 35.6 million people worldwide living with dementia and 7.7 million new cases being diagnosed each year.[1] Alzheimer's disease (AD) is a chronic, slowly progressive and degenerative disease which represents 60%–80% of dementia cases and causes long-term healthcare burdens.[1] Without disease-modifying interventions, the incidence of AD is expected to continue to rise with an ever-ageing global population. With this rise in incidence comes an overwhelming economic burden, with total healthcare costs for the treatment of AD in 2020 reaching US$305 billion.[2]

AD and related dementia are characterised by toxic protein aggregates, with central nervous system amyloid-β (Aβ) plaques and τ neurofibrillary tangles being pathological hallmarks.[1 3 4] The recent discovery of the antimicrobial role of Aβ peptide implicated exogenous pathogens in the development of AD.[3 4] Among the suspected infectious agents, in particular herpesviruses,[5–9] herpes simplex virus type 1 (HSV-1) is the most studied candidate.[8 9] HSV-1 is a common viral infection affecting more than two-thirds of the global population aged 0–49 years in 2016.[10] Most HSV-1 infections are acquired in childhood and are asymptomatic.[10 11] HSV-1 establishes latency in the trigeminal ganglia and has periodic symptomatic reactivations, causing oral ulcerations ('cold sores'), ocular disease (keratitis or retinitis), and more rarely, meningoencephalitis.[11] In the mouse model, inoculation with HSV-1 causes Aβ deposition and other AD-related alterations, with experimentally induced reactivations increasing the hallmark AD pathological changes in a dose-responsive fashion.[12–16] Production of Aβ and intracellular amylin was observed when primary human spinal astrocytes were infected by another neurotropic member of the *Herpesviridae* family, varicella zoster virus (VZV).[17] In addition to the biological findings, several real-world studies have demonstrated an increased risk of dementia in patients diagnosed with HSV-1 and other related neurotropic viruses.[18–22] In the national administrative database from Taiwan, persons diagnosed with HSV-1

clinical disease and treated with antiherpetic drugs had a lower risk of dementia compared with diagnosed and untreated individuals.[20] In Swedish and French medicoadministrative databases, similar protective effects of antiherpetics against dementia were observed in older HSV-infected persons.[18 19]

Although evidence has been largely in support of a role for HSV-1 in AD development, a recent population-based study from the USA reported inconsistent results.[23] An observational study using US-based nationwide real-world data can, therefore, provide valuable insight on the association between HSV-1 and AD. This study aims to investigate the association of HSV-1 infection with AD and AD-related dementia (ADRD) using large administrative claims data from the USA and to assess the potential benefit of antiherpetic medications among patients diagnosed with HSV-1.

METHODS

Data source

IQVIA PharMetrics Plus is one of the largest commercial claims databases in the USA with 215+ million enrollees since 2006.[24] It is a multipayer, closed claims data source with IQVIA's adjudicated medical and pharmacy claims. Data contributors to the database are largely commercial health plans. It contains a longitudinal view of inpatient and outpatient services, prescription and office/outpatient administered drugs, costs and detailed enrolment information. All data are deidentified and anonymised at the patient level and are compliant with the Health Insurance Portability and Accountability Act (HIPAA) to protect patient privacy.[24]

Study design

We conducted a retrospective matched case–control study. Case definition for AD and ADRD was modified from previously published algorithms.[25 26] ADRD included Pick's disease and other frontotemporal dementia, dementia with Lewy bodies, vascular dementia and unspecified dementia. Patients who satisfied at least one of the two following criteria were defined as cases:

1. Two or more AD or ADRD diagnosis codes (see online supplemental table 1 for the International Classification of Diseases (ICD) codes) between 2006 and 2021, at least 30 days apart, or
2. At least one AD or ADRD diagnosis code between 2006 and 2021, followed by at least one ADRD medication (online supplemental table 2) after the first AD/ADRD diagnosis.

Two sets of matching and analyses were conducted for AD cases and ADRD cases, respectively. Cases with AD or ADRD were matched to controls without any history of neurological disorders in a 1:1 ratio on age, sex, region, database entry year, and inpatient and outpatient healthcare visit numbers. The index date for cases was the first AD/ADRD diagnosis date in the database between 1 January 2006 and 30 June 2021. The matched controls were assigned the same index date as their corresponding case. Patients were required to be 50 years or older at the index date.

Diagnoses of HSV-1 and other herpesviruses (HSV-2, VZV and cytomegalovirus (CMV)) prior to the index date were captured using ICD codes (online supplemental table 3). Antiherpetic medications (online supplemental table 4) were mapped to the National Drug Codes (NDC) using IQVIA PharMetrics Plus medication lookup table. Antiherpetic treatments after HSV diagnoses and prior to AD/ADRD index date were captured using the mapped NDC codes to define antiherpetic use status. Antivirals that are rarely used to treat HSV such as ganciclovir, valganciclovir, cidofovir, letermovir and brivudine were not examined.

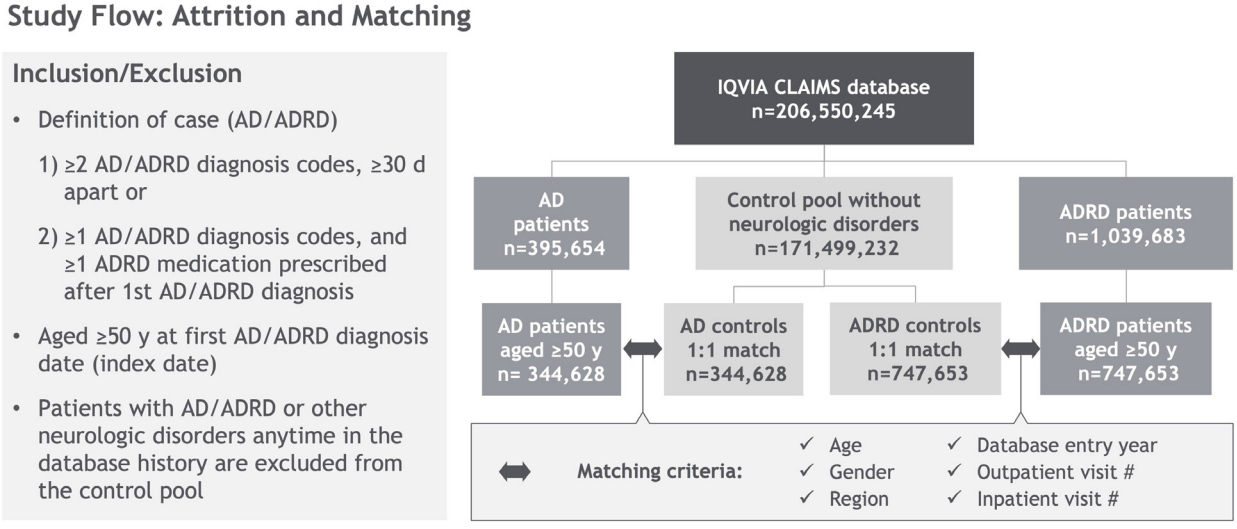


Figure 1 Study design and case–control matching. Cases with AD or ADRD were matched to controls in a 1:1 ratio on age, gender, region, database entry year, and inpatient and outpatient healthcare visit numbers. AD, Alzheimer's disease; ADRD, AD-related dementia.

Table 1 Patient demographic and clinical characteristics

Characteristics	AD case (n=344 628)	Control (n=344 628)	P value
Age			1.0
Mean (SD)	73.39 (5.48)	73.39 (5.48)	
Median (Q1, Q3)	73 (71, 77)	73 (71, 77)	
Age group, n (%)			1.0
50–64	22 991 (6.67)	22 991 (6.67)	
65–74	180 432 (52.36)	180 432 (52.36)	
75+	141 205 (40.97)	141 205 (40.97)	
Gender			1.0
Female	224 378 (65.11)	224 378 (65.11)	
Male	120 250 (34.89)	120 250 (34.89)	
Region, n (%)			1.0
Northeast	78 418 (22.75)	78 418 (22.75)	
Midwest	103 247 (29.96)	103 247 (29.96)	
South	89 231 (25.89)	89 231 (25.89)	
West	73 732 (21.39)	73 732 (21.39)	
Comorbidities, n (%)			<0.0001
None	101 458 (29.44)	119 351 (34.63)	
1	69 603 (20.20)	69 552 (20.18)	
Two or more	173 567 (50.36)	155 725 (45.19)	
CCI			<0.0001
Mean (SD)	2.61 (2.89)	2.41 (2.93)	
Median (Q1, Q3)	2 (0,4)	1 (0, 4)	
Follow-up time, mo			
Mean (SD)	47.86 (46.24)	53.98 (39.97)	<0.0001
Median (Q1, Q3)	33 (9, 74)	48 (24, 72)	
HSV-1, n (%)	1507 (0.44)	823 (0.24)	<0.0001
HSV-2, n (%)	595 (0.17)	364 (0.11)	<0.0001
VZV, n (%)	16 547 (4.80)	11 210 (3.25)	<0.0001
CMV, n (%)	63 (0.02)	67 (0.02)	0.7257
COPD, n (%)	66 241 (19.22)	68 485 (19.87)	<0.0001

AD, Alzheimer's disease; CCI, Charlson comorbidity index; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; HSV, herpes simplex virus; Q, quartiles; VZV, varicella zoster virus.

Conditional logistic regression was used to evaluate the association between HSV-1 and AD/ADRD. The association between antiherpetic medication use and AD/ADRD outcome in the subset of patients with a history of HSV-1 diagnosis was assessed by multivariate Cox proportional hazards (PH) model.

Statistical analysis

The case–control matching had no replacement of matched controls. In the event that multiple controls satisfied the matching criteria, one control was selected randomly.

The index date was defined as described above. In the time-to-event analysis and Cox PH modelling, the follow-up time ended at the earliest of the event of interest, data cut-off or the end of study period (30 Jun 2021).

Odds ratio (OR) for HSV-1 diagnoses and its 95% CI were estimated using conditional logistic regression. Covariates such as age, sex and region were not included in the regression because they were already matched between cases and controls. Comorbidities were adjusted for in the conditional logistic regression model.

When performing Cox PH modelling in the subset of patients who had HSV-1 diagnoses before the AD/ADRD outcome, the relevant covariates (age group, sex, region and comorbidities) were included for confounding

Table 2 Association between HSV-1 and Alzheimer's disease assessed by conditional logistic regression (overall and stratified by age group)

		aOR	95% CI
Overall	HSV-1 vs no HSV-1	1.80	1.65 to 1.96
	One comorbidity vs none	1.30	1.28 to 1.32
	≥2 comorbidities vs none	1.59	1.57 to 1.62
50–70 years	HSV-1 vs no HSV-1	1.14	0.91 to 1.44
	One comorbidity vs none	1.34	1.31 to 1.38
	≥2 comorbidities vs none	1.54	1.50 to 1.59
71–74 years	HSV-1 vs no HSV-1	1.51	1.27 to 1.80
	One comorbidity vs none	1.34	1.31 to 1.37
	≥2 comorbidities vs none	1.45	1.42 to 1.49
≥75 years	HSV-1 vs no HSV-1	2.10	1.88 to 2.35
	One comorbidity vs none	1.23	1.20 to 1.26
	≥2 comorbidities vs none	1.77	1.73 to 1.81

aOR, adjusted ORs; HSV, herpes simplex virus.

adjustment, as the 1:1 matching relationship did not exist between the antiherpetics use group and the no use group in this subpopulation.

Analyses were conducted in SAS Enterprise Guide V.7.1 (SAS Institute) and R V.4.0.5. All analyses were conducted on retrospective, deidentified patient level data.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, conduct, reporting or dissemination plans of this study.

RESULTS

A total of 395 654 patients with AD were identified from the database using the inclusion/exclusion criteria, among which 344 628 were matched to controls on age, sex, region, database entry year, and inpatient and outpatient healthcare visit numbers. The corresponding figures for ADRD were 1 039 683 and 747 653, respectively (figure 1).

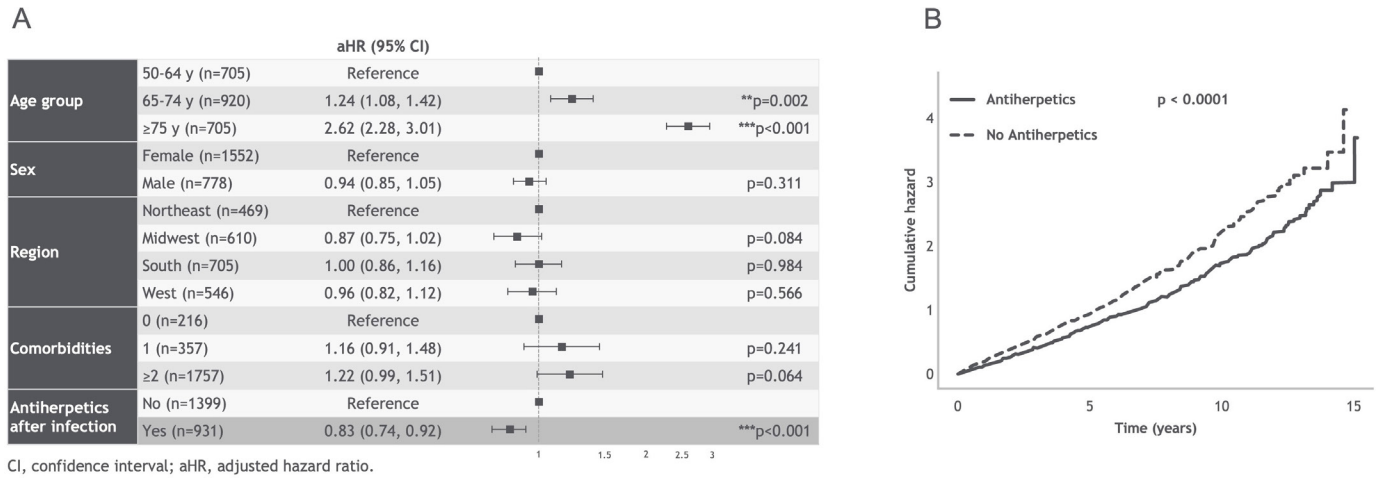
In the AD study population, most patients were women (65%) with a mean age of 73±5 years and had a largely even geographic distribution (table 1 and online supplemental figure 1). Patients with AD had more comorbidities (50% vs 45% with ≥2 comorbidities) and shorter follow-up time (median of 33 vs 48 months) when compared with controls (table 1). A history of HSV-1 diagnosis (online supplemental table 3) was observed in 1507 (0.44%) patients with AD compared with 823 (0.24%) control subjects (table 1). In conditional logistic regression, HSV-1 diagnosis was associated with AD with an adjusted OR 1.80 and 95% CI 1.65 to 1.96 (table 2). In a stratified analysis, this association was found to be more pronounced in older age groups in an incremental manner (table 2, 50–70 years: OR 1.14, 95% CI 0.91 to 1.44; 71–74 years: OR 1.51, 95% CI 1.27 to 1.80; 75+ years: OR 2.10, 95% CI 1.88 to 2.35). Similar results were obtained from the ADRD study population (online supplemental table 5).

Studies have shown that dementia is associated with various viral factors, not limited to HSV-1 alone.[18–20] In light of this, our investigation extended to examine the history of other herpesviruses, including HSV-2, VZV and CMV, within the study population. Furthermore, we explored chronic obstructive pulmonary disease (COPD) as an exposure unrelated to infectious agents. Table 1 illustrates that both HSV-2 and VZV were associated with AD, similar to HSV-1, while no significant difference was observed with CMV between the AD cases and the controls. COPD was found to be higher in controls than in the AD cases (table 1).

In the subset of 2330 patients with a history of HSV-1 diagnoses, 931 (40%) used antiherpetic medications (online supplemental table 4) after being diagnosed. Those who used antiherpetic medications were less likely to develop AD compared with those who did not use antiherpetics (figure 2A, adjusted HR 0.83, 95% CI 0.74 to 0.92, adjusted for age, gender, region and comorbidities). Cumulative hazard of AD among patients with HSV-1 diagnoses was stratified by postinfection antiherpetic medication use with log-rank test. Persons treated with antiherpetics had a significantly decreased risk of AD (figure 2B). Similar protective effects by antiherpetic medications were observed in the ADRD analysis (online supplemental figure 2).

DISCUSSION

AD is an ongoing public health burden with limited interventions available. The association of HSV-1 and AD has been reported previously,[18–22] but there have been conflicting results across various studies.[23] Here,



CI, confidence interval; aHR, adjusted hazard ratio.

Figure 2 The association of antiherpetic medication use with reduced risk of AD. Analyses were performed in the subset of patients with a history of HSV-1 diagnosis. (A) Adjusted Cox proportional hazards model. (B) Kaplan-Meier curve of cumulative hazard of AD. p-value was calculated using log-rank test. AD, Alzheimer's disease; HSV, herpes simplex virus.

we performed a retrospective matched case–control study using the IQVIA PharMetrics Plus claims database. From this analysis, we observed an association of HSV-1 diagnosis with AD, the risk increasing in older patients. Patients above 75 years of age had the highest risk of AD associated with HSV-1. Furthermore, in the subset of patients diagnosed with HSV-1, those using antiherpetics had a significantly reduced risk of developing AD.

The molecular mechanisms underlying the role of HSV-1 and other neurotropic viruses in dementia are still not well understood. However, studies have shown that inflammatory alterations in the brain caused by HSV infection are pivotal in AD development.[27] It has been reported that Aβ peptides are deposited in response to HSV infection and protect host cells by blocking viral fusion with the plasma membrane, pointing to HSV as a potential risk factor for AD.[28] Consistently, Aβ exhibits antimicrobial properties against various pathogens, including HSV-1.[4 28] HSV-1 DNA is present in AD plaques in vivo.[29] Moreover, HSV-1 infection has been reported to induce synaptic dysfunction in cultured neurons via the activation of glycogen synthase kinase 3.[30] Individuals carrying the ApoE ε4 allele, the most common genetic risk factor of AD, are more susceptible to HSV infections.[31 32] While these findings generally corroborate each other, further research is still needed to delineate the HSV-1 signalling pathway in the context of AD pathogenesis.

Our findings presented herein are largely consistent with previous observational studies, but contrast with data reported by Young-Xu *et al*.[23] In this study, no association of HSV infection with AD was observed, but antiherpetic medication was reported to be protective against dementia. One likely cause of this discrepancy is that we performed a matched case–control study rather than a cohort study, resulting in more comparable samples. We also observed an association between AD and HSV-2/VZV, suggesting infection with other neurotropic herpesviruses may increase vulnerability to AD.

Limitations inherent in the use of administrative claims databases are unavoidable in this study. Due to limited data history, HSV-1 infections prior to the patient's database entry were not included in the analysis, and it is possible that some overlap exists between HSV-1 and HSV-2 diagnoses. Under-diagnosis of AD and related dementia, particularly in their early stages, may result in misclassification of cases and controls, potentially diluting the observed association between HSV-1 and AD. Moreover, patients 65 years or older covered by Medicare are often under-represented in claims data, adding complexity to the interpretation of our findings. Additionally, many individuals with HSV-1 infection are asymptomatic, and others may not seek medical care during recurrences and are therefore not clinically diagnosed and recorded in the database. Thus, this study likely captured only a small fraction of the total population with HSV-1 infection. Globally, an estimated two-thirds of the population under 50 are infected with HSV-1. However, precise data on symptomatic HSV-1 infections are limited, as manifestations can be mild or unnoticed. Our results therefore point to HSV monitoring as a potential public health priority for AD management in individuals with a dementia family history.

The similar protective effects of antiherpetics observed in both the AD and ADRD analyses are not surprising, given the overlapping risk factors and potential shared pathological mechanisms between AD and related dementia. Our findings are consistent with earlier studies that have reported comparable associations between antiherpetic use and reduced risk across different dementia types.[18–20] While the molecular mechanisms remain to be fully elucidated, these results are indicative of a possible role for antiherpetic therapy in mitigating dementia risk.

The lack of a significant association between HSV-1 and AD in the 50–70 age group may be due to a lower cumulative infection burden, as HSV-1 reactivations

and their potential neuroinflammatory effects are likely to accumulate over time. Genetic predispositions, such as ApoE-ε4 status, may also interact with HSV-1 differently across age groups, amplifying effects in older populations. Additionally, competing risk factors for AD in this age group, such as vascular disease or metabolic syndrome, might overshadow the contribution of HSV-1. These findings are consistent with studies suggesting that the neurodegenerative impact of HSV-1 becomes more apparent with age and cumulative exposures.[9]

CONCLUSION

In summary, we find an association between symptomatic HSV-1 infection and AD using a large claims database from USA and highlight antiherpetic therapies as potentially protective for AD. These findings place an even greater emphasis on viewing the prevention of herpesviruses as a public health priority. Further research to determine whether suppression of neurotropic viruses can alter the natural history of AD and ADRD is warranted based on the consistent observational studies.

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Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. PharMetrics Plus data may be obtained from IQVIA and are not publicly available. Technical appendix, statistical code are available by contacting the corresponding author.

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