"Decreasing the incidence of dementia through treatment of herpes virus with antiviral therapy"

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Abstract
Background: Dementia is the fifth leading cause of death worldwide with significant effects on healthcare costs and caregiver demands. Therapy up to this point has only shown marginal benefit in delaying the disease. Focus on preventative treatment now is of upmost importance. The link between herpes virus infection and the development of dementia has been well researched, and is an area of focus that may result in preventative therapy. The aim of this study is to assess the efficacy of herpes antiviral treatment in the prevention of dementia.

Methods: An exhaustive search of medical literature, including the databases Medline: Pubmed, ClinicalKey, Web of Science and CINAHL, was completed using the following search terms: alzheimer OR alzheimer's OR dementia AND herpes AND risk AND antiviral OR anti-herpetic. Studies were assessed for quality using GRADE criteria.

Results: A total of 14 articles were screened, 2 of which met inclusion criteria. Both were population-based retrospective cohort studies based in Taiwan. Both studies found a significant association between antiviral therapy for HSV and HZV infections and decreased risk of dementia. Due to the limitations of the current studies further research is required which address a broader population and utilize more sensitive study protocols such as a randomized controlled trial.

Conclusion: Antiviral therapy is associated with a significant decrease in the development of dementia. Further research is warranted to assess the link between these findings.

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Degree Name
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Keywords
Alzheimer dementia, Herpes virus, HSV, HCV, antiviral therapy

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Decreasing the Incidence of Dementia through Treatment of Herpes Virus with Antiviral Therapy

Evan Eisher
and
Stephen Webber

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 2019
Faculty Advisor: Mark Pedemonte, MD
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Biography

Stephen Webber was born in Sandy, UT and attended the university of Puget Sound where he received a bachelor of the arts in Spanish Literature and Psychology. After working as an interpreter and mountain guide in Mexico, he became an EMT-B and worked towards a career in medicine. He was accepted to Pacific University for a Masters in Physician Assistant studies and is currently on clinical rotations in Oregon.

Evan Eisher was born in San Diego, CA and attended California State University, San Marcos where he received a bachelor of the arts in Human Development. Prior to entering the field of medicine, he volunteered as a medical aide for underserved communities in Mexico and Haiti while working in the Emergency Department as an ED Technician. He was accepted to Pacific University for a Masters in Physician Assistant Studies and is currently on clinical rotations in Oregon.
Abstract

**Background:** Dementia is the fifth leading cause of death worldwide with significant effects on healthcare costs and caregiver demands. Therapy up to this point has only shown marginal benefit in delaying the disease. Focus on preventative treatment now is of upmost importance. The link between herpes virus infection and the development of dementia has been well researched, and is an area of focus that may result in preventative therapy. The aim of this study is to assess the efficacy of herpes antiviral treatment in the prevention of dementia.

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Table 1: Quality Assessment of Reviewed Studies

List of Abbreviations

AD        Alzheimer’s Dementia
CCI       The Charlson Comorbidity Index
CINAHL    Cumulative Index to Nursing and Allied Health Literature
ICD-9-CM  International Classification of Disease, Ninth Revision, Clinical Modification
LHID      Longitudinal Health Insurance Database
NHIRD     National Health Insurance Research Database
HSV       Herpes Simplex Virus
HSV1      Herpes simplex virus-1
HZ        Herpes Zoster
HZV       Herpes Zoster Virus
VZV       Varicella Zoster virus
Decreasing the Incidence of Dementia through Treatment of Herpes Virus with Antiviral Therapy

BACKGROUND

Herpes zoster and simplex-1 viruses are among the most prevalent infections in the human population. Herpes simplex-1 (HSV1) is found in ~90% of population worldwide. Varicella zoster virus (VZV), or chickenpox, is the primary infection that leads to the latent infection of herpes zoster (HZ) and can be found in over 95% of the human population over 50 years old. For this reason there is a higher risk for this population in developing HZ. The hypothesis behind the link between herpes virus and dementia has been purported for several decades, with Ball establishing a link between acute herpes encephalitis and Alzheimer’s disease (AD) within the limbic system, an area vital for the utilization of memory recall. The pathological mechanism that was proposed is that fibers from the trigeminal ganglia innervate different vessels and meninges within the region of the limbic system. Latent reactivation of herpes virus, which lays dormant in the trigeminal nerve, may cause an increased risk of developing dementia. More recent research discovered that HSV1 was detected within and may cause the induction of beta-amyloid plaques as well as tau-proteins in human brain tissue, both...
pathological markers of AD. Further research is necessary to determine the exact mechanism of these findings; however, the aforementioned evidence warrants exploration of the link between herpes and dementia.

AD is the most common form of dementia, and it affects over 20 million people worldwide. It is predicted that the prevalence of AD will rise with the growth of the elderly population. It is currently the sixth leading cause of death in the United States. In 2015, healthcare costs associated with dementia in long-term care facilities and hospice care totaled $226 billion. With the increase in incidence and cost of dementia, it is essential that we continue to pursue therapeutic options to delay or diminish its development.

Treatment for AD focuses on the management of symptoms and delaying the progression of the disease. Beneficial outcomes, however, are not consistent. Many of the therapeutic agents that exist today to delay the progression of AD, such as memantine, show marginal improvement in cognitive assessment of patients with dementia. Non-pharmacological treatment focuses on cognitive rehabilitation through exercise and cognitive stimulation and has shown to improve cognitive function in those diagnosed with AD. Although these treatments do mildly improve cognition, their results are temporary
and reveal the need for a more intense focus on the prevention of
dementia. With consistent data showing a strong correlation between
herpes virus infection and the development of dementia, new research
is investigating the possibility of antiviral therapy as an effective
preventative treatment for incident dementia.\textsuperscript{12,13}

The focus of this systematic review will be on studies that show
an association between treatment of herpes virus with antiviral
treatment and subsequent decreased dementia. These studies give
evidence to tailor and develop preventative treatment in those infected
with herpes, which can benefit by way of healthcare savings and
reduced burden on caregivers as well as the potential for vaccine
development in infancy to prevent herpes. Our aim is to determine the
feasibility of these claims and where to direct further research.

\textbf{METHODS}

An exhaustive search of Medline: Pubmed, ClinicalKey, Web of Science
and the Cumulative Index to Nursing and Allied Health Literature
(CINAHL) was completed using the following search terms: alzheimer
OR alzheimer's OR dementia AND herpes AND risk AND antiviral OR
anti-herpetic. Eligibility criteria were broad and required publications to
be written in English and include the outcome of antiviral therapy on
risk of developing dementia. Animal based studies were excluded.
Studies were assessed using GRADE criteria.
RESULTS
A total of 14 articles were reviewed. After screening the abstracts of the available literature there were 2 studies\textsuperscript{12,13} that met inclusion criteria. The 2 articles\textsuperscript{12,13} were population-based retrospective cohort studies. See Table 1. A third controlled laboratory study using animal cell cultures was identified but excluded from analysis due to the limitations of applicability to clinical practice.\textsuperscript{14}

Chen et al

The authors of this study\textsuperscript{12} used a population-based retrospective cohort model to investigate the association between herpes zoster and dementia as well as the role of antiviral therapies in treating herpes zoster and subsequent incident dementia. The selected cases were identified using the ICD-9 CM codes from the National Health Insurance Research Database (NHIRD) in Taiwan. A total of 39205 subjects with herpes zoster were identified and 39205 case control subjects were randomly sampled from the database matching for age, sex, residence and index date, which was the date of herpes zoster diagnosis. Case and control subjects were followed for incidence of any type of dementia including but not limited to senile, vascular, and Alzheimer disease.\textsuperscript{12}

Dementia was defined as 1 inpatient diagnosis or 3 or more outpatient diagnoses. All subjects diagnosed before the index date
were excluded from analysis. The exposure group was defined by use of antiviral therapy for herpes zoster including all formulations of acyclovir, tromantadine, famciclovir, and valacyclovir. The data for drug prescriptions was extracted from the NHIRD and the medication had to be started after the index date for inclusion in the analysis.\textsuperscript{12}

The statistical analysis was done using a Cox regression analysis with competing risk model which adjusted for identified covariate risk factors such as alcohol use disorder, depression and residence. Statistical analysis revealed that of the total subjects 4204 were diagnosed with dementia and 2174 of those were in the herpes zoster cohort. After adjusting for confounding factors such as depression, autoimmune disease and alcohol use disorder there was a statistically significant increased association of dementia for the herpes zoster cohort (adjusted HR: 1.11; 95\% CI, 1.04–1.17). In addition, antiviral therapy was found to significantly reduce the risk of developing dementia with an adjusted HR of 0.55 (95\% CI, 0.40–0.77).\textsuperscript{12}

\textbf{Tzeng et al}

The goal of this study\textsuperscript{13} was to investigate the relationship between HSV infection and dementia as well as the role of antiviral therapy in treating HSV infections and incident dementia. The design of the study was a population-based matched cohort where authors identified participants from the NHIRD and Longitudinal Health
Insurance Database (LHID), 2 widely encompassing health insurance databases in Taiwan. Subjects with an HSV infection were identified using the ICD-9-CM codes, a previously validated means of diagnostic identification. A total of 8362 subjects were selected with the inclusion criteria of age over 50 and newly diagnosed HSV infection, which was marked as the index date. Each case subject was frequency matched for sex, age and index date with 3 case control subjects from the NHIRD.\(^{13}\)

The authors accounted for multiple covariates including age, sex, residence, income and Charlson Comorbidity Index (CCI). The CCI includes 3 common risk factors for the development of AD, which are diabetes, cerebrovascular disease and stroke. Antiviral therapy was defined by use of acyclovir, famciclovir, ganciclovir, idoxuridine, penciclovir, tromantadine, valaciclovir or valganciclovir.\(^{13}\)

Participants were followed for a 10-year period until onset of dementia, which was defined as Alzheimers, vascular or other dementia. Statistical analysis was done using the Fisher exact to determine cohort differences, after adjusting for covariates a multivariate Cox proportional hazards regression showed that subjects with genital or non-genital HSV infections were at a statistically higher risk of developing any type of previously defined dementia. A total of 7215 participants on antiviral therapy were compared to a subgroup of
1147 participants not on antiviral therapy. Patients on any type of antiviral treatment were associated with a decreased risk of overall dementia (adjusted HR 0.092, 0.079-0.108, P < 0.001). Investigators did note the differences between the populations of treatment subgroups. Those on antivirals tended to live in higher urban areas in Northern Taiwan and were associated with greater CCI scores.\textsuperscript{13}

**DISCUSSION**

Dementia remains one of the leading causes of death worldwide, with burden on caregivers and the healthcare system being a major driving force to discovering therapeutic options to delay or prevent the disease. Therapeutic interventions thus far have been limited to supplements, medications, and cognitive therapy, which have only shown marginal improvement in delaying the progression of the disease. It is therefore imperative to seek out and discover preventative options that can relieve patients, families, and caregivers from this devastating disease. A link between herpes virus and dementia has been well established and continues to be an area of focus in the prevention of dementia. With the prevalence of herpes virus affecting over 90 percent of the population, there is potential to reach a practice changing preventative intervention. This analysis aims to determine the efficacy of antiviral treatment as a potential preventative option and where to direct further research.
This extensive systematic review found 2 articles\textsuperscript{12,13} which showed an association between decreased risk of dementia and treatment of HSV or HZV infections with antiviral therapy. Both articles were population-based cohort studies, which extracted data from the NHIRD in Taiwan. The major difference between the 2 articles was the case subject variable, HSV\textsuperscript{13} versus HZV\textsuperscript{12} infections. The NHIRD is one of the world’s largest health insurance databases and accounts for over 99\% of Taiwan’s population. For that reason it is a very comprehensive database for research purposes but applicability to a larger population remains questionable. Although both studies\textsuperscript{12,13} were able to show a statistically significant link between antiviral therapy and decreased risk of dementia, the participant population is specific to Taiwanese residents, which increases the possibility of confounding variables such as diet, genetics or even climate.

A GRADE analysis rated both articles as moderate quality because although both studies revealed a large magnitude of effect of antiviral therapy, their nature as observational studies implies inherent limitations for that effect. Another limitation to these studies is the unclear mechanism by which herpes is related to the development of dementia. Although research has shown beta-amyloid plaques and tau proteins with herpes DNA in brain tissue, there remains the fact that other infectious diseases, such as\textit{ Helicobacter pylori}, may contribute
to the development of dementia. Further research must be established discovering the mechanism behind herpes infection and dementia; however, our analysis reveals a large effect between treating herpes and preventing dementia, thus suggesting a link.

Despite the limitations of these studies, further research is required as both have shown a significant correlation for decreasing the incidence of overall dementia. This association has also been shown in a laboratory study which found that the use of antiviral agents, acyclovir and pencyclovir, decreased the accumulation of Aβ and P-tau, proteins associated with AD, in cell cultures acutely infected with HSV1.

The overall results of this review indicate the need for further research. Prospective cohort studies utilizing antiviral therapy and placebo controls are warranted based on the results of current research. Future studies should be conducted outside of Taiwan to decrease the likelihood of confounding variables contributing to the aforementioned results. Although these studies do not provide conclusive evidence for the use of anti-herpetic therapy in the direct prevention of incident dementia, there is no reason to avoid treating latent herpes outbreaks with antivirals as any potential risks are low.
CONCLUSION

Dementia is a leading cause of death worldwide with no effective treatment options available. A number of diseases and co-morbid conditions have been linked to the development of dementia, most recently HSV1 and HZV infections. This review investigated the efficacy of treating patients with herpes virus outbreaks with antiviral therapy as a means of decreasing the likelihood of developing dementia later in life. Two studies were found which both uncovered a significant association between herpes-targeted antiviral therapy and decreased risk of developing dementia. Further research is warranted in the form of prospective cohort studies and randomized controlled trials utilizing antiviral therapy and placebo controls. Continued research could solidify this important discovery in preventative treatment of dementia for patients with HSV1 or HZV.
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\textsuperscript{a}RR decreased for patients on anti-herpetic medication
\textsuperscript{b}Patient population is specific to Taiwan so may have unseen confounding variables
\textsuperscript{c}Prescriptions of antiviral therapy were associated with a reduced risk of developing dementia following the diagnosis of herpes zoster (HR =0.55; 95% CI, 0.40–0.77).