Journal of Molecular and Genetic Medicine

ISSN: 1747-0862

Sasmita et al., J Mol Genet Med 2018, 12:4
DOI: 10.4172/1747-0862.1000388

Mini Review Open Access

Emerging Links between Herpesviruses and Alzheimer's Disease Pathology

Sasmita AO*, Methi A and Kislai P

Göttingen Graduate School for Neurosciences, Biophysics and Molecular Biosciences, Georg-August-Universität Göttingen, Göttingen, Germany

Abstract

Over 3.7 billion people worldwide under the age of 50 are estimated to have some form of Herpes simplex virus (HSV) infection in their lifetime. Despite mostly presenting as asymptomatic, HSV infection has been associated with worsening symptoms and biological conditions in various diseases, some of which are neurological, such as Alzheimer's disease (AD). This mini-review thus aims to showcase the varying researches carried out in the past decades which sought the connection between the infection and the neurodegenerative disease. Various members of the *Herpes viridae* family have been associated with worsening AD pathology and symptoms, namely HSV-1, HSV-2, human herpes virus 6 (HHV-6), and HHV-7. The virus affects many aspects of the nervous system to promote neurodegeneration, including fragmentation of amyloid precursor proteins (APP), inducing production of excess amyloid beta (Aβ) in response to the viral infection, and formation of tau neurofibrillary tangles (NFT), all of which point to further degeneration of the nervous system structures and cognitive decline in AD patients. HSV has been significantly reported to induce concurrent alterations in the context of AD. Although more in-depth analysis still needs to be done to consider other factors such as age, viral load, and the degree of neurodegeneration, HSV infection remains an interesting drug target through the means of antivirals in ameliorating a certain degree of neurodegeneration, cognitive decline, and memory loss in AD.

Keywords: Alzheimer's disease; Herpes simplex virus; Interferon; Neurodegeneration

Introduction

Overview of Herpes Simplex Virus (HSV) and Alzheimer's Disease (AD)

Herpes simplex virus 1 (HSV-1) is a member of the *Herpes viridae* family of viruses with double stranded DNA and a genome size of 152 kb encodes at least 84 different polypeptides [1]. It is a common neurotropic virus that affects most humans and it is implicated for its infection an etiology in Alzheimer's disease (AD), a common neurodegenerative disease which is characterized by cognitive decline which leads to memory loss and dementia. The aim of this mini-review is to highlight current and relevant studies which considered the correlations between HSV infection and AD pathology at molecular and genetic levels.

The primarily affected brain regions by this infection are the frontal and cortical cortices which are also mainly damaged in AD [2]. Moreover, inflammation markers found in AD and many inflammatory mediators involved in HSV-1 infection are common. For example, tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), IL-8, and interferon-inducible protein 10 which are elevated in the brain of AD patients are also produced upon infection with HSV-1 virus [3,4]. Using PCR, it was discovered HSV-1 DNA is present in high amount in the brains of elderly individuals including patients with AD when compared to non-patients [5].

It was observed that HSV-1 confers a high risk of developing AD when in the brain of individuals carrying specific allele for gene APOE-the APOE-ε4 allele [6,7]. Amyloid plaques and neurofibrillary tangles (NFT) are the two abnormal features observed in AD patients. Plaques are composed of amyloid-β. It is derived from the proteolytic cleavage of amyloid-β protein precursor (APP) [8]. Tau, a microtubule associated protein is the main part of NFT formed by the hyper-phosphorylation by many enzymes including protein kinase A and glycogen synthase kinase 3β. HSV-1 codes for a protein which is homologous to PKA [9]. Malfunction in autophagy has also been shown in the presence of HSV infection which would lead to the accumulation of protein which might shed some light on the presence of aberrant proteins in AD [10,11]. The reason behind autophagic dysfunction remains unclear in AD; however, the role of HSV-1 in degrading host cell proteins is a defense mechanism against invading pathogens and to counteract this, the pathogens have co-evolved to restrict autophagy [12].

Current evidence of link between HSV and AD

In the past decade, evidences of infectious agents playing a role in the progression of AD have been continuously emerging, one of which is HSV [13]. Within current literature, the role of HSV-1, otherwise known as 'oral herpes' in AD pathogenesis have been more commonly studied; although some studies also showed other types of the virus possibly having implications in AD, namely HSV-2, human herpesvirus 6 (HHV-6), and HHV-7 [14-16]. This section summarizes current knowledge of how HSV infection may be correlated with AD with Figure 1 constructed to visualize a brief overview on how HSV has been observed to interact with worsening AD pathology.

HSV-1

Aside from AD, HSV-1 infection has been linked to worsening symptoms in various other neurodegenerative diseases and the mechanisms of HSV-1 mediating production of toxic protein aggregates commonly found in neurodegenerative diseases are continuously being researched [17,18]. Within the context of AD, HSV-1 promotes neurodegeneration through the upregulation of Aβ, tau protein, and

***Corresponding author:** Andrew Octavian Sasmita, Göttingen Graduate School for Neurosciences, Biophysics and Molecular Biosciences Georg-August-Universität Göttingen Grisebachstr, 537077 Göttingen, Germany, Tel: +49 178 5467495; E-mail: andrewoctavians@gmail.com

Received November 22, 2018; **Accepted** December 18, 2018; **Published** December 22, 2018

Citation: Sasmita AO, Methi A, Kislai P (2018) Emerging Links between Herpesviruses and Alzheimer's Disease Pathology. J Mol Genet Med 12: 388 doi:10.4172/1747-0862.1000388

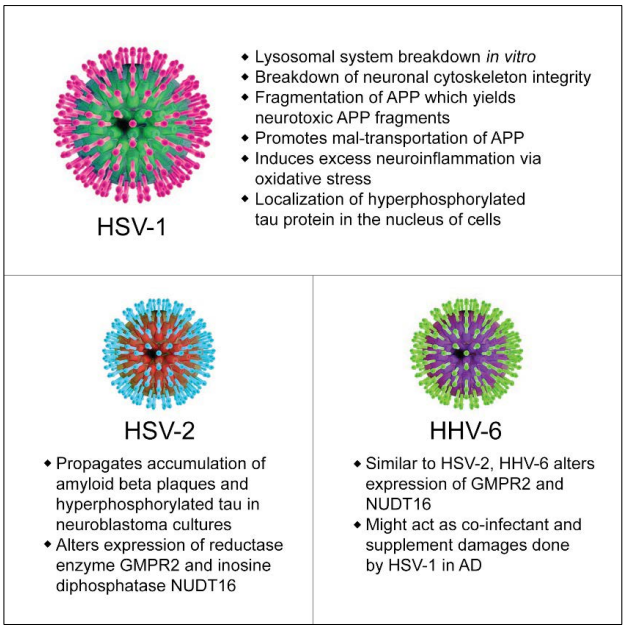

Figure 1: Brief overview of relevant members of the *Herpes viridae* family in the context of AD and their proposed mechanisms actions.

oxidative stress amongst the many other AD hallmarks [19]. Recently, the breakdown of lysosomal systems within *in vitro* cultures has also been debated as a novel potential mechanism as to how HSV-1 infection may induce AD hallmarks [19]. The cytoskeleton integrity of neuronal cultures infected by HSV-1 are also affected and this might shed some light in the cellular and mechanical disruption that happens during the process of neurodegeneration [20].

Within the Aβ hypothesis, HSV-1 was observed to induce fragmentation of APP which is neurotoxic much like its downstream form, Aβ plaques [21]. Intracellular HSV-1 components have also been reported to interact with APP, increasing and reducing APP's speed during interplay and thus, causing a mal-transportation of APP within infected cells [22]. Other more popular theories regarding the mechanism of HSV-1 in AD is that the virus directly stimulates the production of more Aβ deposits [23]. HSV-1, which can become latent in the body, may be reactivated and suppresses the immune system aside from inducing excess inflammation, further worsening AD [24]. Eimer, et al. have also recently come up with an argument that Aβ is produced to mediate viral infection among many other infection types and that prolonged Aβ production would eventually lead to neurodegeneration observed in AD [15,25].

Tau hyperphosphorylation and formation of NFT have been shown in various studies to be affected by HSV-1. Similarly, to Aβ, most of the tau produced via HSV-1 mediation was shown to localize within the nucleus of affected cells [26]. Within *in vitro* studies, it was also revealed that HSV-1 growth is not dependent on the expression of tau, signifying HSV-1's role as a cause of worsening tau pathology in AD [26]. Cleavage of tau protein at aspartic acid residue 421 was also shown to induce production of tau aggregates commonly seen in AD and other neurodegenerative diseases [27].

Other *Herpes viridae* family members

Within preclinical studies, it was observed that HSV-2, otherwise known as the 'genital herpes' propagates worsening hallmarks of AD in the form of accumulated Aβ plaques and hyperphosphorylated tau in neuroblastoma cultures [28]. A recent study conducted by Readhead et al. which employed multiscale analysis of AD network unravelled that HSV-6 and HSV-7 disrupted genetic and molecular components of the APP metabolism component of the brain [14]. They also found that certain other members of the HSV family, namely HSV-2 and HHV-6A, can alter the expression of certain proteins that regulate nucleotide expression, such as the reductase enzyme GMPR2 and inosine diphosphatase NUDT16 respectively. This suggests that viruses from the HSV family can induce dysregulation of nucleotide pool metabolism, and these observations are congruous with previous metabolomics studies conducted for AD [29].

Additionally, many studies have provided strong evidence that primary human herpesvirus 6 or HHV-6 is present, and can be successfully detected, not only in a large number of AD patients but also in the brains of healthy elderly patients and multiple sclerosis patients [30-33]. Wozniak et al. were able to detect the HHV-6 antibody in CSF in 22% of AD patients, but not in samples from healthy individuals [34]. In one of their earlier studies, they also found the prevalence of HHV-6 in AD patients at a much higher frequency (72%) as opposed to healthy samples (40%). Although there was a significant overlap between HHV-6 and HSV-1 in AD samples, it was also observed that APOE 34 expression was high in both HHV-6-positive and HHV-6-negative AD patients, in contrast to results obtained for HSV-1 positive samples [32]. In a nutshell, these findings suggest that HHV-6 by itself might not be a risk factor for AD but might possibly enhance or activate other co-infectants or supplement the damage done by HSV-1 in AD patients [35].

However, contrary to the evidence above, there are studies that have suggested that many members of the Herpesviruses family, such as HSV-2 AND HHV-8, have no association with AD pathogenesis [36,37]. There have been experiments conducted to determine if there is any causal relationship between herpesviruses and sporadic AD, and many groups have failed to show any such link [36-38]. Nonetheless, these negative results can very well be the consequence of low sensitivity of the techniques or methods used in these studies, which could lead to non-detection of viral genomes or antigens in AD samples [30]. Hence, taking into account all the strong evidence illustrated earlier, it can be strongly suggested that there is a link between HSV, especially HSV-1, and development of AD in patients. Given the strong correlation between HSV-1 and AD pathology, more attention should also be given to other *Herpes viridae* members to identify if such AD-propagating mechanisms are exclusive to only some of the viral subtypes.

Future Directions

Targeting HSV infection has been an emerging trend in the quest to combat AD with antivirals being employed in clinical studies, such as an interventional clinical trial of valacyclovir in AD patients who are tested positive for HSV-1 or HSV-2 [39]. A Taiwanese study which recruited 33,448 HSV-positive subjects also reported a marked reduction of AD dementia in HSV-positive from 28.33% in the non-treated patient group to 5.8% in the antiviral-treated group [40]. Among the antivirals being employed, acyclovir, valciclovir, and valganciclovir caused the most significant reductions of AD dementia scores [40]. In the future, more proteomic and transcriptomic data could be produced to further delineate the connection between the two. The causal-effect relationship between components of the infection and the neurodegenerative disease should also be further researched as curing HSV infection might only tackle one side of the many problems that AD present.

Conclusion

Large scale population studies report over 2.7 times likelihood of developing AD dementia in the presence of HSV infection. This figure and prevalence of the viral infection itself make HSV an interesting drug target to combat AD amongst many other neurodegenerative diseases. This mini-review summarizes current research which reported correlations, positive and negative, between HSV and AD. Mounting evidence has been gathered throughout the past decades and dealing with HSV infection might just be a new avenue in the great effort to combat AD.

References

1. McGeoch DJ, Dalrymple MA, Davison AJ, Dolan A, Frame MC, et al. (1988) The complete dna sequence of the long unique region in the genome of herpes simplex virus type 1. J Gen Virol 69: 1531-1574.
2. Ball MJ (1982) Limbic predilection in Alzheimer dementia: Is reactivated Herpesvirus involved? Can J Neurol Sci 9: 303-306.
3. Cacquevel M, Lebeurrier N, Chéenne S, Vivien D (2004) Cytokines in neuroinflammation and Alzheimer's disease. Curr Drug Targets 5: 529-534.
4. Lokensgard JR, Hu S, Sheng W, VanOijen M, Cox D, et al. (2001) Robust expression of TNF-alpha, IL-1beta, RANTES, and IP-10 by human microglial cells during non-productive infection with herpes simplex virus. J Neurovirol 7: 208-219.
5. Jamieson GA, Maitland NJ, Wilcock GK, Craske J, Itzhaki RF (1991) Latent Herpes simplex virus type 1 in normal and Alzheimer's disease brains. J Med Virol 33: 224-227.
6. Itzhaki RF, Lin WR, Shang D, Wilcock GK, Faragher B, et al. (1997) Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. Lancet 349: 241-244.
7. Lin WR, Wozniak MA, Esiri MM, Klenerman P, Ithzaki RF (2001) Herpes simplex encephalitis: Involvement of apolipoprotein E genotype. J Neurol Neurosurg Psychiatry 70: 117-119.
8. Blennow K, De Leon MJ, Zetterberg H (2006) Alzheimer's disease. Lancet 368: 387-403.
9. Benetti L, Roizman B (2004) Herpes simplex virus protein kinase US3 activates and functionally overlaps protein kinase A to block apoptosis. Proc Natl Acad Sci 101: 9411-9416.
10. Nixon RA, Wegiel J, Kumar A, Yu WH, Peterhoff C, et al. (2005) Extensive involvement of autophagy in Alzheimer disease: An immuno-electron microscopy study. J Neuropathol Exp Neurol 64: 113-122.
11. Yu WH, Kumar A, Peterhoff C, Kulnane SL, Uchiyama Y, et al. (2004) Autophagic vacuoles are enriched in amyloid precursor protein-secretase activities: Implications for β-amyloid peptide over-production and localization in Alzheimer's disease. Int J Biochem Cell Biol 36: 2531-2540.
12. Itzhaki RF, Wozniak MA (2008) Herpes simplex virus type 1 in Alzheimer's disease: The enemy within. J Alzheimers Dis 13: 393-405.
13. Sochocka M, Zwolińska K, Leszek J (2017) The Infectious etiology of alzheimer's disease. Curr Neuropharmacol 15: 1-2.
14. Readhead B, Haure-Mirande JV, Funk CC, Richards MA, Shannon P, et al. (2018) Multiscale analysis of independent alzheimer's cohorts finds disruption of molecular, genetic, and clinical networks by human herpesvirus. Neuron 99: 64-82.
15. Eimer WA, Kumar VDK, Shanmugam NNK, Rodriguez AS, Mitchell T, et al. (2018) Alzheimer's disease-associated β-amyloid is rapidly seeded by *Herpes viridae* to protect against brain infection. Neuron 99: 56-63.
16. Hemling N, Röyttä M, Rinne J, Pöllänen P, Broberg E, et al. (2003) Herpesviruses in brains in Alzheimer's and Parkinson's diseases. Ann Neurol 54: 267-271.
17. Zhou L, Miranda-Saksena M, Saksena NK (2013) Viruses and neurodegeneration. Virol J 10: 172.
18. Caggiu E, Paulus K, Galleri G, Arru G, Manetti R, et al. (2017) Homologous HSV1 and alpha-synuclein peptides stimulate a T cell response in Parkinson's disease. J Neuroimmunol 310: 26-31.
19. Kristen H, Sastre I, Muñoz-Galdeano T, Recuero M, Aldudo J, et al. (2018) The lysosome system is severely impaired in a cellular model of neurodegeneration induced by HSV-1 and oxidative stress. Neurobiol Aging 68: 5-17.
20. Zambrano A, Solis L, Salvadores N, Cortés M, Lerchundi R, et al. (2008) Neuronal cytoskeletal dynamic modification and neurodegeneration induced by infection with herpes simplex virus type 1. J Alzheimers Dis 14: 259-269.
21. De Chiara G, Marcocci ME, Civitelli L, Argnani R, Piacentini R, et al. (2010) APP processing induced by herpes simplex virus type 1 (HSV-1) yields several app fragments in human and rat neuronal cells. PLoS One 5: e13989.
22. Cheng SB, Ferland P, Webster P, Bearer EL (2011) Herpes simplex virus dances with amyloid precursor protein while exiting the cell. PLoS One 6: e17966.
23. Wozniak MA, Itzhaki RF, Shipley SJ, Dobson CB (2007) Herpes simplex virus infection causes cellular β-amyloid accumulation and secretase upregulation. Neurosci Lett 429: 95-100.
24. Itzhaki RF (2018) Corroboration of a major role for Herpes simplex virus Type 1 in alzheimer's disease. Front Aging Neurosci 10: 1-2.
25. Kumar DKV, Choi SH, Washicosky KJ, Eimer WA, Tucker S, et al. (2016) Amyloid-β peptide protects against microbial infection in mouse and worm models of Alzheimer's disease. Sci Transl Med 8: 340.
26. Álvarez G, Aldudo J, Alonso M, Santana S, Valdivieso F (2012) Herpes simplex virus type 1 induces nuclear accumulation of hyperphosphorylated tau in neuronal cells. J Neurosci Res 90: 1020-1029.
27. Lerchundi R, Neira R, Valdivia S, Vio K, Concha MI, et al. (2011) Tau cleavage at D421 by caspase-3 is induced in neurons and astrocytes infected with Herpes Simplex Virus Type 1. J Alzheimer's Dis 23: 513-520.
28. Kristen H, Santana S, Sastre I, Recuero M, Bullido MJ, et al. (2015) Herpes simplex virus type 2 infection induces AD-like neurodegeneration markers in human neuroblastoma cells. Neurobiol Aging 36: 2737-2747.
29. Kaddurah-Daouk R, Rozen S, Matson W, Han X, Hulette CM, et al. (2011) Metabolomic changes in autopsy-confirmed Alzheimer's disease. Alzheimers Dement 27: 309-317.
30. Honjo K, Van Reekum R, Verhoeff NPLG (2009) Alzheimer's disease and infection: Do infectious agents contribute to progression of Alzheimer's disease? Alzheimer's Dement 5: 348-360.
31. Gordon L, McQuaid S, Cosby SL (1996) Detection of herpes simplex virus (types 1 and 2) and human herpesvirus 6 DNA in human brain tissue by polymerase chain reaction. Clin Diagn Virol 6: 33-40.
32. Lin WR, Wozniak MA, Cooper RJ, Wilcock GK, Itzhaki RF (2002) Herpesviruses in brain and Alzheimer's disease. J Pathol 197: 395-402.
33. Luppi M, Barozzi P, Maiorana A, Marasca R, Torelli G (1994) Human herpesvirus 6 infection in normal human brain tissue. J Infect Dis 169: 943-944.
34. Wozniak MA, Shipley SJ, Combrinck M, Wilcock GK, Itzhaki RF (2005) Productive herpes simplex virus in brain of elderly normal subjects and Alzheimer's disease patients. J Med Virol 75: 300-306.
35. Qavi HB (2003) Possible role of HHV-6 in the enhanced severity of HSV-1 keratitis. *In vivo* Std 13: 427-32.
36. Pogo BG, Casals J, Elizan TS (1987) A study of viral genomes and antigens in brains of patients with Alzheimer's disease. Brain 110: 907-915.
37. Pogo BG, Elizan TS (1985) Search for viral DNA sequences in Alzheimer brain tissue. Lancet (1: 978-979.
38. Middleton PJ, Petric M, Kozak M, Rewcastle NB, McLachlan DR (1980) Herpes-simplex viral genome and senile and presenile dementias of Alzheimer and Pick. Lancet 1: 1038.
39. https: //www.clinicaltrials.gov/ct2/show/NCT03282916.
40. Tzeng NS, Chung CH, Lin FH, Chiang CP, Yeh CB, et al. (2018) Anti-herpetic medications and reduced risk of dementia in patients with herpes simplex virus infections-A nationwide, population-based cohort study in Taiwan. Neurotherap 15: 417-429.