Advances in
Biotechnology & Microbiology
ISSN 2474-7637

Juniper Publishers
key to the Researchers

Opinion
Volume 8 Issue 4 - March 2018
DOI: 10.19080/AIBM.2018.08.555743

Adv Biotech & Micro

Herpes Simplex Virus as a Cause of Alzheimer's Disease

Modhusudon Shaha[1,2]*

[1]*Medical Microbiology/Virology Unit, School of Medical Sciences, The University of Manchester, UK*

[2]*Microbial Biotechnology Division, National Institute of Biotechnology, Bangladesh*

Submission: March 06, 2018; **Published:** March 09, 2018

***Corresponding author:** Modhusudon Shaha, Microbial Biotechnology Division, National Institute of Biotechnology, Ganakbari, Savar, Dhaka-1349, Bangladesh, Tel: +8801728228201; Email: msshaha146@gmail.com

Abstract

Alzheimer's disease (AD), a chronic neurodegenerative disorder is caused due to the neurological imbalance of an individual. Although AD was documented decades ago, its actual reason is out of description yet. Several factors such as dementia, obesity, age, etc. have been documented to be responsible for AD; however, viral associations need to be demonstrated. In this opinion, I would describe the association of herpes simplex virus with AD.

Opinion

Alzheimer's disease (AD) is a chronic neurodegenerative disorder, which can be preferably characterized by dementia occurring 60-70% of all cases [1]. AD is more likely a progressive disease consisting of three critical stages (the first-stage starts with confusion, middle-stage with disorientation, aphasia, depression and hallucination, and later-stage with symptoms like dysplasia and severe dementia) and involves language problems, disorientation, behavior issues, etc. [2-4]. Globally, there have been 46.8 million cases of dementia with 9.9 new cases every year [5]. Although, AD is thought to be mostly genetic, the actual reason is behind the screen and still unknown.

As the disease is due to the neurological imbalance, the risks may not be limited to genetic or body's functional abnormalities caused by injuries, depression, hypertension, etc. [6]. Therefore, other environmental risk factors such as viral infections that are associated with exposure to central nervous system (CNS), for instance, herpes simplex virus (HSV), are thought to have the potential impact on the development of AD [7]. HSV is a double-stranded DNA virus, which locates at sensory ganglia as latent form after primary or initial infection [7]. It has been documented that HSV maintains a quiescent but persistent form in sensory ganglia by expressing latency associated transcript (LAT) RNA [8]. However, it is still unknown whether LAT encodes proteins to cause AD or HSV itself stimulates gradual functional loss of neurons in this stage of latency. Nevertheless, neurological symptoms caused by AD such asaphasia, dysphasia, confusion, etc. are mostly similar to that of HSV infection [4,9].

Severe loss of memory is caused by both types of AD, namely rare early-onset AD (EOAD causing 1-6% of all cases) and frequent late-onset AD (LOAD), which are prevalent among 30-65 years and 60-65 years respectively [10]. Heritance relations were found in both types of AD, which is mainly diagnosed by amyloid plaques and neuro fibrillary tangles [11]. Furthermore, several studies documented the abnormalities of thetype-4 allele of apolipoprotein E (APOE4) in the brain of AD patients [11-13].

From the history, the concept of herpes simplex viral association with AD was proposed decades earlier [14,15]. However, still now there is no confirmed evidence of HSV association regarding AD; though, it is assumed that the reactivation of HSV1 can cause increased formation of β-amyloid, a characteristic feature of AD, by direct and inflammatory damage of the CNS [11]. Moreover, several studies confirmed the presence of HSV1 DNA in the brain of AD patients [16,17]. They also suggested the association of HSV-1 DNA with abnormalities of APOE4 [16,17].

Neuropathologically, the brain of patients with AD is normally suffered by the presence of hallmarks such as the neuro fibrillary tangles that are composed of hyper-phosphorylated Tau proteins, and the β-amyloid protein aggregates located in the cortex and hippocampus area [17]. Tau protein is thought to be phosphorylated by enzymes such as protein kinase A, induced by HSV1, and β-amyloid protein aggregates (plaques) are found mixed with the HSV1 DNA in most of the cases of AD as documented [18]. According to a study in Manchester, 90% of

the β-amyloid plaques contain HSV1 DNA, of which 72% were directly associated with plaques [16], suggesting the possible association of HSV1 with developing AD.

In regards to the Tau proteins, these are the aberrantly phosphorylated forms of microtubules associated proteins, otherwise called neurofibrillary tangles [18]. Such abnormal phosphorylation of Tau proteins occurs at several sites of amino acids, such as serine 202, threonine 212, serine 214, serine 396 and serine 404 residues by host enzymes, namely protein kinase A and glycogen synthase kinase 3-β [18]. However, the production of these enzymes in host brain is induced by HSV1, which may further clarify the association of HSV1 with developing AD [18].

From very past, it has been thought that the only risk factors for developing AD were age, brain injury, Down syndrome and the abnormalities of APOE4 [10]. But since several decades, viral association with AD has been highlighted and AD has been predicted to be multi factorial [19]. Usually, the human immune system has some autophagy properties, which is the natural, regulated and destructive mechanism prevent in assembling of unnecessary or dysfunctional components of the immune system as well as degradation of cellular components, and ultimately, their recycling in the body [20]. However, HSV1 has been documented to disrupt autophagy in the body and therefore, prevents the destruction of these abnormal proteins, which then leads to their deposition and accumulation in the brain, and finally, the development of AD [20]. To other extends, antivirals used against HSV1 such as acyclovir, have been found to have obstructive effects on progressing AD and most effectively, together with an intravenous immunoglobulin (IVIG) as documented by several studies [11,21].

From the previous supports, it can be claimed that HSV1 may have a strong association with developing AD. Now, it is still unclear that 'which stage of HSV1 infection is responsible for developing AD'. If we think about the replication stages of HSV1, a primary or initial infection of a susceptible host is involved, which may either be symptomatic or asymptomatic [22]. Symptomatic infections may cause either mild symptoms which normally does not need to meet with doctors, sometimes called semi-symptomatic infections, or an acute symptomatic infection. Symptomatic acute cases are noticeable and can easily be treated using antiviral or other existing treatments. However, asymptomatic or semi-symptomatic cases may be in high risks of developing AD due to the lack of detection at an early stage and hence, development ofHSV1 latency, although viruses with acute infection can undergo latency as observed in several cases [23,24]. In this stage of latent infection, the virus is not usually detectable due to the production of LAT RNA only [8]. However, it is still unknown whether viruses prepare themselves at this stage to cause AD. Furthermore, several studies documented the presence of IgM and IgG antibody to HSV1 in the blood of AD patients, which suggests a recent HSV1 infection [17]. Now it also needs to know whether it is a primary or recurrent infection. Several studies reported thatHSV1 may also migrate to the brain during primary infection suggesting that primary infection might be able to cause AD by infecting CNS in the brain [7,15,25]. On the other hand, it could also be a recurrent HSV1 infection, as the chance of formation of β-amyloid is likely more during recurrent infections, at which, LAT transcripts along with active mRNAs would be detect able in the brain [26]. In recurrent infection, HSV1 comes out of sensory ganglia to the peripheral nervous system due to the stress, immunodeficiency of the host, other viral or bacterial infections, exposure to UV light, etc., and may cause infections with increased severity of pneumonia, encephalitis, etc. [11,26].

Other than HSV1, several human herpes viruses such as HSV2, human herpes virus 6 (HHV6) and cytomegalovirus (CMV) were also been documented to be associated with AD [11]. The prevalence of HHV6 is much higher than HSV1 in the brain of AD patients compared to the normal people, although not found to be directly associated with the development of AD [11,27]. The presence of HSV2 and CMV in AD patients does not signify to cause AD, although detected in their brain [11]. Unlike HSV1, other herpes viruses detected in patient's brain were not found to have an impact on APOE4 abnormalities and hyper-phosphorylation of Tau proteins [27]. However, further researches with other herpes viruses are needed to identify whether they have possible effects on the development of AD.

In conclusion, the above-presented data may indicate a strong association of HSV with the pathogenesis of AD by accumulating β-amyloid aggregates into plaques, hyper-phosphorylating Tau proteins required to form neurofibrillary tangles, and disrupting autophagy in the human brain. Other viruses might cause few of similar symptoms like β-amyloid, but HSV is unique among the elderly population by developing recurrent infections. Therefore, greater attention should be paid to the environmental factors, especially herpes simplex viral infection contributing to causing AD.

References

1. Holtzman DM, Morris JC, Goate AM (2011) Alzheimer's disease: the challenge of the second century. Sci Transl Med 3(77): 77sr1.
2. Klimova B, Maresova P, Valis M, Hort J, Kuca K (2015) Alzheimer's disease and language impairments: social intervention and medical treatment. Clin Interv Aging 10: 1401-1407.
3. Fatemi Y, Boeve BF, Duffy J, Petersen RC, Knopman DS, et al. (2011) Neuropsychiatric aspects of primary progressive aphasia. J Neuropsychiatry Clin Neurosci 23(2): 168-172.
4. Baquero M, Martin N (2015) Depressive symptoms in neurodegenerative diseases. World J Clin Cases 3: 682-693.
5. D'Onofrio G, Yu Z, Forlenza OV (2016) Alzheimer's Disease and Cognitive Frailty: Novel Therapeutic Technologies. Biomed Res Int 2016: 7242651.
6. Hung SC, Liao KF, Muo CH, Lai SW, Chang CW, et al. (2015) Hearing Loss is Associated With Risk of Alzheimer's Disease: A Case-Control Study in Older People. J Epidemiol 25(8): 517-521.

How to cite this article: Modhusudon Shaha. Herpes Simplex Virus as a Cause of Alzheimer's Disease. Adv Biotech & Micro. 2018; 8(4): 555743. DOI: 10.19080/AIBM.2018.08.555743.

7. Conrady CD, Drevets DA, Carr DJ (2010) Herpes simplex type I (HSV-1) infection of the nervous system: is an immune response a good thing? J Neuroimmunol 220(1-2): 1-9.
8. Nicoll MP, Hann W, Shivkumar M, Harman LE, Connor V, et al. (2016) The HSV-1 latency-associated transcript functions to repress latent phase lytic gene expression and suppress virus reactivation from latently infected neurons. PLoS Pathog 12(4): e1005539.
9. Gilden DH, Mahalingam R, Cohrs RJ, Tyler KL (2007) Herpes virus infections of the nervous system. Nat Clin Pract Neurol 3(2): 82-94.
10. Bekris LM, Yu CE, Bird TD, Tsuang DW (2010) Genetics of alzheimer disease. J Geriatr Psychiatry Neurol 23(4): 213-227.
11. Itzhaki RF (2014) Herpes simplex virus type 1 and Alzheimer's disease: increasing evidence for a major role of the virus. Front Aging Neurosci 6: 202.
12. Liu CC, Liu CC, Kanekiyo T, Xu H, Bu G (2013) Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol 9(2): 106-118.
13. Verghese PB, Castellano JM, Holtzman DM (2011) Apolipoprotein E in Alzheimer's disease and other neurological disorders. Lancet Neurol 10(3): 241-252.
14. Itzhaki RF, Wozniak MA (2008) Herpes simplex virus type 1 in Alzheimer's disease: the enemy within. J Alzheimers Dis 13(4): 393-405.
15. WuDunn D, Spear PG (1989) Initial interaction of herpes simplex virus with cells is binding to heparan sulfate. J Virol 63(1): 52-58.
16. Wozniak MA, Mee AP, Itzhaki RF (2009) Herpes simplex virus type 1 DNA is located within Alzheimer's disease amyloid plaques. J Pathol 217(1): 131-138.
17. Piacentini R, De Chiara G, Li Puma DD, Ripoli C, Marcocci ME, et al. (2014) HSV-1 and Alzheimer's disease: more than a hypothesis. Front Pharmacol 5: 97.
18. Wozniak MA, Frost AL, Itzhaki RF (2009) Alzheimer's disease-specific tau phosphorylation is induced by herpes simplex virus type 1. J Alzheimers Dis 16(2): 341-350.
19. Harrison PJ (1986)0 Pathogenesis of Alzheimer's disease--beyond the cholinergic hypothesis: discussion paper. J R Soc Med 79(6): 347-352.
20. Itzhaki RF, Cosby SL, Wozniak MA (2008) Herpes simplex virus type 1 and Alzheimer's disease: the autophagy connection. J Neurovirol 14(1):1-4.
21. Wozniak MA, Itzhaki RF (2010) Antiviral agents in Alzheimer's disease: hope for the future? Ther Adv Neurol Disord 3(3): 141-152.
22. Dasgupta G, Chentoufi AA, Kalantari M, Falatoonzadeh P, Chun S, et al. (2012) Immunodominant "asymptomatic" herpes simplex virus 1 and 2 protein antigens identified by probing whole-ORFome microarrays with serum antibodies from seropositive asymptomatic versus symptomatic individuals. J Virol 86: 4358-4369.
23. Minami M, Kita M, Yan XQ, Yamamoto T, Iida T, et al. (2002) Role of IFN-gamma and tumor necrosis factor-alpha in herpes simplex virus type 1 infection. J Interferon Cytokine Res 22(6): 671-676.
24. Nicoll MP, Proenca JT, Efstathiou S (2012) The molecular basis of herpes simplex virus latency. FEMS Microbiol Rev 36(3): 684-705.
25. Shieh MT, Spear PG (1994) Herpes virus-induced cell fusion that is dependent on cell surface heparan sulfate or soluble heparin. J Virol 68(2): 1224-1228.
26. Fan S, Cai H, Xu X, Feng M, Wang L, et al. (2017) The characteristics of herpes simplex virus type 1 infection in rhesus macaques and the associated pathological features. Viruses 9(2): E26.
27. Lin WR, Wozniak MA, Cooper RJ, Wilcock GK, Itzhaki RF (2002) Herpes viruses in brain and Alzheimer's disease. J Pathol 197:395-402.

DOI: 10.19080/AIBM.2018.08.555743

How to cite this article: Modhusudon Shaha. Herpes Simplex Virus as a Cause of Alzheimer's Disease. Adv Biotech & Micro. 2018; 8(4): 555743. DOI: 10.19080/AIBM.2018.08.555743.