World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: http://www.wjpsonline.org/
Review Article

Viral and bacterial causes for Alzheimer's disease: increasing evidence for a major role of infectious agents

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Received: 19-09-2017 / Revised Accepted: 18-10-2017 / Published: 01-11-2017

ABSTRACT

The growing experimental data points to chronic viral and bacterial infections are possible risk factors for AD disease. Virus and bacteria are normally latent in elderly brains but reactivates under certain conditions cause persistent CNS infections by continuous pathogen replication. In depth viral and microbial agents have been reported to produce molecular hallmark of neurodegeneration, such as production and deposit of misfold protein aggregates, synaptopathies and neuronal death. HSV1 DNA plays major evidence in viral AD. Chlamydia pneumonia antibodies present in brain tangles are major evidence in bacterial AD. The infections may be synergy with recognized risk factors such as aging, concomitant metabolic diseases and host specific genetic signature. This review will focus on the contribution given to neurodegeneration by Herpes simplex type-1 and Chlamydia pneumonia.

Key Words: Herpes simplex type-1, Neurodegeneration, Chlamydia pneumonia, Alzheimer's disease.

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How to Cite this Article: G. Rajeswari, A. Dishanth, G. Rupa, M. Hari Priya and P. Sowjanya. Viral and bacterial causes for Alzheimer's disease: increasing evidence for a major role of infectious agents. World J Pharm Sci 2017; 5(11): 100-105.

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia in elderly. This condition occur after 5th decade of life and its incidence progressively increases with advanced age. The exact cause is not known but few factors are implicated in its etiology which includes positive family history and deposition of Aβ amyloid derived from amyloid precursor protein (APP) forming neuritic senile plaques and neurofibrillary tangles. AD is associated with neuronal loss and progressive synaptic dysfunction, accompanied by the deposition of amyloid-(A) peptide, a cleavage product of the amyloid-protein precursor (APP), and abnormal forms of tau protein, markers that have been used as diagnostic criteria for the disease[1,2]. These constitute the hallmarks of AD, but whether they are causes of AD or consequences of AD is unknown. We suggest that these are indicators of an infectious etiology. In the case of AD, it is often not realized that microbes can cause chronic as well as acute diseases; that some microbes can remain latent in the body with the potential for reactivation, the effects of which might occur years after initial infection. AD has emerged as a serious public health concern, placing an immense burden on the individual, family, community, and health care resources. When developing diagnoses and treatments of complex illnesses, like Alzheimer's disease, most of the battle lies in finding of causative agent.

The transitional period between normal cognitive functioning and dementia is referred to as Mild Cognitive Impairment (MCI)[11] the most common form, the one most likely to progress to AD, is amnestic MCI (a-MCI). Patients with a MCI present with memory deficits greater than would be expected based on age and education; however functional abilities remain relatively preserved and independence intact[12]. Estimates of the annual incidence of individuals with MCI progressing to dementia range from 5 to 15[13]. Regardless of this variation, annual conversion rate of those with MCI is far greater than the baseline incidence rate[14].

Researchers and clinicians had worked on Alzheimer's disease (AD) and related topics, expressed their concern that one particular aspect of the disease has been neglected, even though treatment based on it might slow or arrest AD progression. They referred many studies, mainly on humans, implicating specific microbes in the elderly brain, notably herpes simplex virus type1 (HSV1), Chlamydia pneumoniae, and several types of spirochaete, in the etiology of AD[3-6]. Fungal infection of AD brain[7,8] has also been described, as well as abnormal microbiota in AD patient blood[9]. The first observations of HSV1 in AD brain were reported almost three decades ago[10]. The ever-increasing number of these studies (now about 100 on HSV1 alone) warrants re-evaluation of the infection and AD concept.

VIRAL INFECTION AND ALZHEMERS DISEASE

HSV-1 is an ubiquitous neutropic virus. On chronic and persistent exposure to HSV-1 it has been proposed as potential risk for AD. It may vary from country to country about 1/3rd of the population has recurrent clinical manifestations of HSV-1 infection. It affects around 56%-85% of world population. Epidemiological studies suggests that another potential risk factors for AD is the presence of the HSV-1 genome in post-mortem brain specimens from AD, particularly those who carry type IV allele gene that encodes apolipoprotein E4[15,16]. HSV-1 reactivation genes detected in the brains of patients with familial AD are associated with β-amyloid deposits in patients suffering from AD[17,18]. HSV-1 DNA has found in amyloid plates from the temporal and frontal cortices. Recently a large population based study showed that anti HSV-1 IgG antibodies which are the markers of primary or reactivated HSV-1 are the risk factor for HSV-1 infections[19]. HSV-1 infections are increased in elderly patients with positive titers of anti HSV-1 antibodies while it is not associated with anti HSV-1 IgG antibodies, which are markers of a lifelong infection. Finally genome wide association (GWA) studies have correlated individual brain susceptibility to HSV-1 infection with a genetic risk of AD[20,21]. Entry of HSV-1 into host cell is mediated by nectin-2. Nectin-2 is also known as herpes virus entry meditor-B or polio virus receptor related protein-2, Apo lipoprotein–E particularly its 4th allele gene is established as genetic risk factor for AD, has also been shown to influence susceptibility to viral infections and spreading into neuronal cells variations in the outer mitochondrial damage induced by HSV-1 DNAase such as UL12.5 and other genes. Variations in genetic signature determines individual brain susceptibility to HSV-1 infection during ageing or pathogen driven damages leading to neuro degenerations.

BACTERIAL INFECTIONS AND ALZHIEMERS DISEASE

AD was first linked to c.pneumoniae infection based on the evidence that 90% of AD brains were found to be PCR-positive for c.pnemoniae pathogen, particularly in the cerebral regions most affected by AD[22]. This microorganism is able to infect microglia, astrocytes, peri vascular

macrophages and myocytes[22,23]. The microorganism is isolated from the tissue as metabolically active and propagated in cells. Some studies failed to detect c.pneumonia in archival tissue of AD patients, but two of these studies were performed on tissue that was paraffin embedded, which may have effected the organism identification using specific PCR technique[24-26]. Other studies were performed on frozen tissue, and identified presence of c.pneumoniae in AD patient brain through PCR analysis. Recently, little et al demonstrated that C.pneumoniae in mice induced AD like hall marks in brains through intranasal inoculation. C.pneumoniae antibodies have been identified in AD brain, tangles and colocalizing with plaques in vulnerable brain regions[27].

EVIDENCE FOR INFECTION

1. In most of the elderly people, viruses and other microbes are present in the brain[28-30]. Usually dormnant, reactivations occur after stress and immunosupresson. Eg: HSV1 DNA is amplified in the brain of immunocompresed patients[31].
2. Herpex simplex encephalitis (HSE) damages localized regions of the CNS related to limbic system, associated with cognitive, memory and affective processes as well as personality[32].
3. HSV infection revealed by seropositively is associated with development of AD[35-37].
4. In brain of AD patients, pathogen signatures (Eg: HSV1 DNA) specifically colocalize with AD patients[30, 33, 34].
5. AD is known to have a prominent inflammatory component characteristic of infection.
6. AD risk factors include polymorphisms in the apolipoprotein E (ApoE) gene (which modulates immune system) and susceptibility to infectious disease.
7. Genome-wide association studies reveal that immune system components including virus receptor genes are further AD risk factors.
8. Features of AD pathology are transmissible by inoculation of AD brain to primates and mice.

GROWING EVEDENCE FOR MECHANISM: ROLE OF Aβ

(i) Enzymatic product like 25- hydroxyl cholesterol, 25- OHC induces innate anti viral immunity and the gene encoding cholesterol 25-hydroxylase is selectively up regulated by virus infection[38, 39].

(ii) Polymorphisms in human CH25H govern both AD susceptibility and a deposition[40], arguing that Aβ induction is likely to be among the targets of 25OHC, providing a potential mechanistic link between infection and Aβ production[41]

(iii) Potent activity against multiple bacteria is an A β anti microbial peptide and yeast[42]. Also has antiviral activity[43, 44].

(iv) Antimicrobial peptide like (defensin1) is up regulated in AD brain[44].

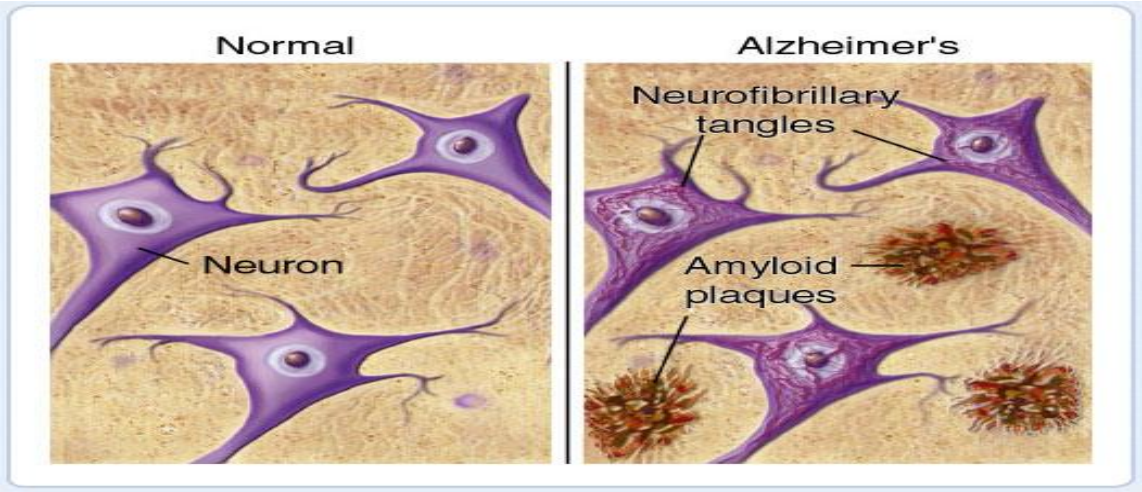
EVIDENCE OF REACTIVATION OF HSV1 IN THE HUMAN CNS

The gross damage caused during HSE is far more readily detectable. A major problem in studying the role of HSV1 in AD is the current lack of a method for detecting reactivation of the virus particularly if, as postulated, it occurs on a limited scale or in very localized regions of the CNS outbreak. After the initial episode a number of case reports of HSE recurring during some month and years. It has been suggested that these might be fairly frequent occurrences of sub-clinical encephalitis because of the mildness might not be diagnosed correctly. HSV test was sent to a reference laboratory for analysis 3200 CSF specimens' by peter & several from the subjects with wide range of ages. They found that over-all, 26 were positive for HSV1 and 36 for HSV2, but in the over 60 age group, the ratio of HSV-2–HSV-1 infection was low, namely, 3:13, and 11 of the 13 HSV1-positive subjects were female. In the over 70 s, comprising 1 male, 10 female, 10 were positive for HSV-1, with 1 female positive for HSV2. Almost infections were detected in females than in male twice as many as HSV1 and HSV2. Female aged over 70 years data display commented on particulars bias for HSV1 CNS infection an intriguing ending, in view of the preponderance of females with AD. Condition such as immunosuppressant strongly suggests that HSV1 reactivates in post-mortem human brain specimens under pre PCR study. By using a 3H-HSV1 probe incites hybridisation was examined in patients brain acute leukaemia who had been immune suppressed as part of the treatment. Strong labelling of indicating the presence of HSV1 DNA, was revealed in frontal and temporal cortices of those who were HSV-sero positive but not in those who were HSV-sero negative or who had not been immune suppressed[45]. Nov 2004 and December 2012 revealed that a review of multiple sclerosis patient was treated with natalizumab which hinders inflammatory cell migration into the CNS indicates the presence and reaction in patients brain with HSE under 20 cases which are developed.

CONCLUSION

The evidence shows that presence of HSV1 for reactivation, its interference with cellular process,

its harmful effects on cognition is very strong in the elderly human brain. HSV1 is a very good support for being a causative factor in AD. The virus and bacteria induced effects add to and are possibly amplified by several factors such as metabolic disorders, genetic alterations and other environmental risk factors, involved in the pathogenesis of neurodegenerative diseases. As a result, the virus and bacteria induced damage amplifies and accelerates the neurodegenerative process, whose signs are usually manifested during aging. The data reviewed in our paper suggest that more detailed understanding of the molecular mechanisms underlying virus and bacteria mediated neuronal damage may have the way to the identification of new preventive and/or therapeutic strategies aimed at counteracting the progression of these devastating pathologies.



Neurofibrillary tangles in Alzheimers Disease

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