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Alzheimer's disease and the role of infectious Agents: A review

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ABSTRACT

Alzheimer's disease (AD) is considered as a neurodegenerative disease in elderly people. Several hypotheses have been proposed in the development of AD. Infection with pathogenic agents such as viruses can be one of these hypotheses. In this review, data on the possible association between the infectious agents and AD has been collected and summarized. The current study revealed that infectious agents express proteins (pentapeptides or more) with obvious homology to beta-amyloid protein (Aβ) and amyloid precursor protein (APP). Hitherto, infection with pathogens such as herpes simplex virus type 1 (HSV-1), picornavirus, Borna disease virus, cytomegalovirus (CMV), Epstein Barr virus (EBV), or human herpes virus 6 (HHV-6) have been reported to be associated with the pathophysiology of AD. These researchers suggest that some infectious agents, may contribute to the pathogenesis of AD. Therefore, with the prevention and treatment of such infectious agents the sanitation authorities can decrease the risk of AD.

KEY WORDS: Alzheimer Disease, Viruses, Neurodegenerative Diseases, Adjustment Disorders, Bacteria.

1. INTRODUCTION

Alzheimer's disease (AD) is considered as one of the most common types of neurodegenerative disease and dementia in the brain mainly in people over 65 years (Sun, 2012; Wang and Ding, 2008; M.R. and Cohen, 2013) with no cure known for it at the moment (Itzhaki, 2014). It is expected that 5.2 million Americans have AD so that it is the sixth reason of death in U.S. (Thies, 2013; Weiner, 2012). AD has been recorded with the prevalence of 20 million people in 2001 all over the world with double estimated rate every 20 years (Hampel, 2011; Carbone, 2014). The most common form of dementia, sporadic AD, usually develops in late stage of life with multifactorial causation (JC, 2002; Gorelick, 2004). Behavioral and psychological symptoms in AD patients embrace confusion, poor judgment, language disturbance, agitation, withdrawal, hallucinations, delusions, aggression, wandering, dementia, apathy, depression and sleep disorders (Geda, 2013; Hayashi, 2010). Microscopic examination of the brain indicates the pathological lesions correlated with AD – doddering plaques and neurofibrillary tangles, the lesions that have been originally described by Alzheimer (Song and Wang, 2010; Hartig, 2010). Additionally, many various lesions have been reported within the brain of AD patients. Senile plaques occur extra cellularly and square measure are distinguished in the hippocampus and cortex of AD sufferers. Their main part is a beta-amyloid protein (Aβ) which could be a peptide that is between thirty-nine and forty-three amino acids long. The forty (Aβ 1–40) and forty-two (Aβ 1–42) amino alkanoic acid variants of Aβ constitute the predominant forms which are found in plaques. Aβ is one amongst the proteolytically cleaved product of amyloid precursor protein (APP), the gene of which is found on chromosome 21 (Soontornniyomkij, 2010; Hampel, 2010). Cleavage of APP involves three enzymes referred to as the secretases (termed a-, b- and c-secretases). The b- and c-secretases are considered for generation of Aβ (a-secretase doesn't generate Aβ however instead cleaves APP to provide soluble APP (sAPP) and because the a-secretase cleavage site is found within the Aβ fragment, such cleavage makes generation of Aβ impossible). Already, the well-known risk factors for AD are age, Down's syndrome and head injury. Infective agent participation theory within the pathological process of AD was 1st planned in, 1977 as a result of evidences of a number of the pathological changes in AD which were similar to those that were seen in 2 particle illness Crow and Creutzfeldt-Jacob diseases (CJD).

Since AD occurs in one out of each five people, it is likely that a viral agent may play a task in its development. For instance, it has been found that CNS secondary effects of rubella or measles solely occur in an exceedingly tiny range of genetically inclined people. Additionally, HSV can undergo the traditional barriers of the body and with penetrating to the peripheral systema nervosum which leads to acute encephalitis. Epidemiological data over the years, strengthening the possible connection between HSV-1 infection and development of AD. Detection of HSV-1 and viral DNA in brain autopsies of AD patients specifically within amyloid plaques and presence of anti-HSV antibodies in numerous studies would be strongly suggestive of association between HSV-1 infection and Alzheimer's disease.

Numerous over tropism viruses like rabies, picornaviruses, cytomegalovirus and choriomeningitis virus induce inflammatory responses which cause death of the host cell (Kittur, 1992). Without knowledge of all the risk

factors involved in AD, the disease may not effectively be prevented or cured. The aim of the current review is to focus attention for the association of infectious agents with pathophysiology of AD in more details.

2. METHODS

Published studies were accessed through the Scopus, Medline and PubMed search engines were used for this article. Search terms used were "Alzheimer disease", "viruses", "infectious disease medicine", "bacteria" and "amyloid". Only English-language papers were considered.

3. RESULTS

3.1. Herpes simplex virus type 1: Herpes simplex virus-1 (HSV-1), is a member of Herpesviridae family which may cause diseases ranging from oral herpes to severe encephalitis. Herpes infection has been concerned in inflicting severe diseases in neonates, elderly, transplanted patients immunosuppressed by drugs and in patients with immune deficiency syndrome (Khajeh, 2011; Ghannad, 2014). HSV-1 can also infect the human central nervous system (CNS) latently (Gordon, 1996). Further clarification has been revealed that HSV-1 resides within the peripheral nervous system (PNS) in most adults, typically within the trigeminal ganglia, where it sporadically reactivates (Dobson and Itzhaki, 1999). The HSV pandemics can be intense and create a serious public health threat (Emami, 2009). In herpes simplex encephalitis, the virus affects the identical areas in AD (frontal and temporal cortices and hippocampus) (Robinson, 2004; Jamieson, 1991; GA, 1992; Beffert, 1998; P, 1993; Carbone, 2014; MJ, 1982; Itzhaki, 2004; Wozniak, 2005; Denaro, 2003). The HSV-1 DNA have often seen fewer in young than in older individuals' brains. In older people, virus may enter the brain more than young people because of the decline in the immune system with aging. Numerous investigation have been undertaken in the last twenty years that have confirmed a relationship between HSV-1 and AD (Jamieson, 1991; GA, 1992; Wozniak, 2005; Sequiera, 1979; Itzhaki, 1997; Lin, 2002; K, 2009). Further studies demonstrated that AD possibly can be caused by accumulative injury over a prolonged period of time due to HSV-1 propensity for latency and sporadically reactivating. This can inflict more injury in some cases. HSV-1 causes a serious acute, but rare, neurologic condition as herpes simplex encephalitis (MJ, 1982). Significantly, the etiology of encephalitis can be separated into two major causes; autoimmune-mediated encephalitis probably caused by vaccination or a recent viral infection and/or also infection-related encephalitis by attack of pathogenic infectious agents directly (Sabouri, 2013). Viral antigen can be detected in the hippocampus, cingulate gyri amygdala, and olfactory tracts necrosis of the frontal and/or temporal lobes occurs in initial stages of this disease (the areas affected in AD). Based on the results which have been published, it might speculate that HSV-1 affect the exact same cells that are devastated in AD (MJ, 1982).

3.2. The influence of APOE genotype on the HSV-1 infection: Apolipoprotein E (APOE), as a protein–lipid complex has an initial role in lipid transport and tissue repair. APOE clearly increases the possibility for AD. The HSV-1 infection and APOE allele together act synergistically as risk factors for Alzheimer. APOE has been considered to have a role in viral attachment to cells. APOE genotype may affect either the degree of injury following HSV-1 reactivation or influence in tissue repair. Moreover, APOE-e4 carrier may have an effect on the HSV-1 replication cycle (Reinvang, 2013; Chang, 2013; TT, 2012; Rohn, 2012).

3.3. Epstein Barr virus: Epstein Barr virus (EBV), a member of β- herpesvirina family, has been reported to infect over 90% of the adults globally. The replication of EBV and CMV induce cytokine production which might influence general inflammation. Elevated pro-inflammatory cytokines are associated to several age-related diseases together with cancer, Type 2 diabetes and AD. EBV and Cytomegalovirus (CMV) replication can induce production of IL-6 IL-8, IL-1b and tumor necrosis factor-alpha (TNF-a) in cultured cells via reactivation of EBV. Early viral proteins induce macrophages in contact with endothelial cells to provide pro-inflammatory cytokines that are involved in up regulation expression of endothelial adhesion molecules (Bennett, 2012; Rasolabadi, 2015).

3.4. Cytomegalovirus: The seroprevalence of CMV as a common infection have been reported in most of the world's population. The rate of CMV seroprevalence is reported higher in those of people living in lower socioeconomic societies (Bate et al., 2010) which increases with age in older people. Any harm to the developing CNS represents the serious consequence of innate herpes infection. The correlation of CMV with impaired detection in the body has been cleared in the people with pre-existing clinical conditions, such as AD, cardiovascular disease and schizophrenia (Gow, 2013; Bale, 2012).

The recent researches show that chronic infection of CMV might affect immune system and lead to aggravate age-related diseases such as atherosclerosis, rheumatoid arthritis, and AD. CMV infection severely impairs the T cells via increasing the number of CMV-specific CD8+CD28- T cells (Ouyang, 2004; Almanzar, 2005). These lymphocytes accelerate the amount of pro inflammatory cytokines which will worsen the functional pathology and cause disorders, such as AD in older people (Wick, 2000). Post mortem, brain specimens from patients with vascular dementia (VaD) have been investigated for HSV-1, CMV, and HHV-6 DNA by polymerase chain reaction that showed 93% of the VaD patients harbor CMV DNA. This work described that CMV, one of the two viruses that

most powerfully was involved as a potential cause in coronary heart disease (CHD) was reported in a very high rate brains of VaD patients but the rate of harboring HSV-1 and HHV-6 were the same (WR, 2002).

3.5 Human herpes virus-6: Human herpes virus-6 (HHV-6), types A and B have the potent to affect the brain (Challoner, 1995; Gordon, 1996). HHV-6 causes exanthema subitum, a common childhood disease that sometimes attacks to the CNS causing meningitis and encephalitis (Huang, 1991; JA, 1995). HHV-6 frequency is far higher in AD patients (72%) than in healthy brains (40%) with a meaningful relationship, therefore, HHV-6 may be a risk factor for AD. However, HHV-6 and HSV-1 have been a remarkable overlap in more than half of AD brains but APOE frequency was higher in HSV-1 positive AD patients than the healthy individuals (Lin, 2002). In addition, HHV-6 antibody was not in the CSF of healthy individuals but was reported in the CSF of 22% of AD patients (Wozniak, 2005).

3.6. Other Viruses and Alzheimer:

3.6.1. Borna Disease virus: Borna Disease virus (BDV) infects various animal species and can cause disorders in behavior and cognitive functions so that sometimes cause a fatal neurologic disease. Some studies indicate the relationship between BDV and the human mental disorders (Bode, 1995; Staeheli, 2000). For instance, a study showed the presence of Borna antibodies in the serum specimens of 16 out of 979 in the mental patients and no antibody in 200 healthy people. This indicated the possibility of the Borna virus role in mental disorders in humans (Rott et al., 1985). In addition, regarding to AD-like disorders, there is a report which cleared a correlation between BDV infection and spatial learning ability defects in rodents (Sauder, 2001). Moreover, another research reported that CRNP5 as a BDV variant rapidly induced severe neural diseases in rats whereas, CRP3, another variant, stimulated slower and milder disease on behavior. In conclusion, infection to BDV, irrespective of the variant, increases transforming growth factor beta 1 (TGF-b1) expression in the brain which seems to be correlated with the beginning of a variety of neurological diseases, including AD and Parkinson's disease (Nishino, 2009; Nishino, 2002).

3.6.2. Picornaviruses: Picornaviruses are a family of RNA viruses including rhinoviruses, enteroviruses, aphthovirus and Hepatovirus. They can cause polio, colds, diarrhea, cardiovascular infection, and meningitis. Picornaviruses might infect the CNS of wide host species (K, 2009; EJ, 2006). Picornaviruses induce the death of neuron cell by changing the apoptotic mechanism of host cells to establish persistent infections, then, viral proteins of poliovirus such as protease 3C may induce apoptosis in host cells (Buenz and Howe, 2006).

3.6.3. Influenza virus: The olfactory bulb (OB) which is a common target in neural diseases such as AD or multiple sclerosis, is a way for what that the viruses inhale from the air and kill neurons (Majde, 2010). Some viruses can replicate in neurons and spread from neuron to neuron such as influenza virus that may be passively transported to the bulb via the OB (unknown mechanism), and is taken up by glial cells in the outer layers of the bulb (JA, 2007). It is revealed that common viruses which are encountered in our daily life may initiate neuro inflammation via olfactory neural tracts. Therefore, the causation of neurological disease by a persistent neurovirulent viral infection is that over a person's lifetime, multiple 'common cold' and 'flu-like' viruses attack the brain from the nasal passages via the olfactory nerves.

3.6.4. HIV-1: The human immunodeficiency virus is a lentivirus of the Retroviridae family that causes acquired immunodeficiency syndrome (AIDS), a condition in which the body become vulnerable to infection because of the immune system damages by HIV virus (Borjabad and Volsky, 2012). HIV-associated neurocognitive disorders (HAND) is a common manifestation of HIV infection. HAND includes a wide range of neurological disorders such as AIDS dementia complex, HIV-associated encephalopathy and AIDS-associated cognitive decline. Atrophy of neurites and neuronal loss in the same damaged areas of the brain of an AD patient is the histopathological sign of HIV-infected brains (Borjabad and Volsky, 2012). Borjabad and Volsky (2012) conducted a meta-analysis study and concluded that brains of patients with HAND and AD have similar mis-regulated gene expression profiles suggesting neuroimmune responses and progressive deficits in synaptic transmission (Widera, 2014).

3.6.5. Prions: Prion diseases are a group of progressive neurodegenerative conditions that can occur in both animals and humans. They are driven by an uncommon type of self-replicating microbe and are very similar to AD (Pogue, 2014). After being inoculated into susceptible host, Aβ induce widespread amyloid genesis (Prusiner, 2013). Recently, it was discovered that prions can act as an Aβ receptor and facilitate amyloid neurotoxicity so that Aβ can attach to peripherally administrated prions and make its way easier into the brain. Thus, it could be concluded that prions probably have an involvement in AD-like signaling processes such as neuroinflammation, synaptic degeneration and amyloid genesis (Borjabad and Volsky, 2012).

3.7. Chlamydophila pneumonia and other pathogenic bacteria: In recent years, a higher attention has been paid to the possible role of the pathogenic bacteria such as Chlamydophila. pneumoniae of the family Chlamydiaceae, which causes pneumonia, in diseases such as coronary artery disease, arthritis, multiple sclerosis, meningoencephalitis, and AD (Hammond, 2010). For instance, according to the identification of C. Pneumoniae antigens in the neocortex of AD brain and also by considering the role of antigens such as senile plaques (*SP*) and

neurofibrillary tangles *(*NFT), it can be inferred that C. Pneumoniae infection may be a contributory factor in AD pathology (Choroszy-Krol, 2014). It is worth mentioning that pneumonia rather than AD is the main cause of death among people who suffer from AD (Hill, 2014). Interestingly, other studies have strongly suggest the correlation of Borrelia species, Helicobacterpylori, the periodontopathic spirochaete Treponema denticola, Tannerella forsythia, Porphyromonas gingivalis and other bacteria with increased incidence of age-related dementias including AD (Miklossy, 2011). In spite of the fact that pathogens such as Chlamydia Pneumoniae, HSV-1, HHV-6, cytomegalovirus, and Helicobacter pylori have a substantial impact on the progression of AD, there are other agents that can act as a cause of this process as well (Schillinger, 2004; Wozniak, 2005).

3.8. Fungal infection of the CNS: In the recent years, it has been found that there exists many fungus material (such as proteins, polysaccharides and disseminated and diffuse mycoses) in the peripheral blood of AD patients; suggesting that chronic fungal infections can be a contributory factor in AD (Liu, 2008).

3.9. Toxoplasma and neurodegeneration: Toxoplasma species such as Toxoplasma gondii are obligate, intracellular, parasitic protozoan that can lead to neurological dysfunction and encephalitis by chronically developing inflammation of the brain and CNS. Lately, an association has been found between increased anti-T.gondii antibodies and AD, leading to the assumption that T. gondii infection may play a role in AD (Prandota, 2014).

3.10. Molecular mechanism and the role of pathogens: There are many other genes and proteins of HSV, which could have an important impact on AD during its life cycle such as a synergistic effect between host and pathogen, which are effective in the pathology of AD. In this regard, two transcription factors including POU domain, class 2, transcription factor 1 (POU2F1) and the CP2 transcription factor(TFCP2) genetically are related to AD and can be exemplified as proteins which are directly involved in the HSV life cycle. POU2F1 causes viral activation through combining by the viral enhancer complex, while APP and low-density receptor-related protein 1 (LRP1) bind to the viral genome and modulate gamma-secretes TFCP2. The binding of host transcription factors to the viral genome targets [(e.g. Beta-secretase 2 **(**BACE2), Lipoprotein lipase (LPL), the oxidized lipoprotein receptor (OLR1) or Glycogen synthase kinase 3 beta (GSK3B)] can also influence the pathology of AD (CJ, 2008). Moreover, HSV mediates many genes in AD by which it has the ability to meddle in apoptosis. HSV-1 virus can bind to all types of cholesterol transporter plasma lipoprotein, which by this mechanism the virus can spread into the brain. Accordingly, these lipoproteins, their receptors, cholesterol transporters and cholesterol-related enzymes are contributed to AD (Carter, 2007). Moreover, the contributory effect of mitochondrial DNA deletion as a part of the normal aging mechanism has been demonstrated in previous studies (Corral-Debrinski, 1994; Blanchard, 1993). This phenomenon, and analogous ones can be induced by viral infection via the herpes simplex protein called UL12, a *5*'- to 3'-exonuclease encoded by herpes simplex virus type 1, or by an N-terminally truncated version of the UL12 gene, called UL12.5, which deletes mitochondrial DNA (Saffran, 2007).

Additionally, some studies have been indicated that AD is a systemic inflammatory disease (Britschgi and Wyss-Coray, 2007). The long-term stimulation of the immune system lowers the CD8+T cells. Moreover, CD8+T cells express the co-inhibitory receptor, killer-cell lectin like receptor G1 (KLRG1) and cluster of differentiation 57 (CD57) which are sometimes designed as "senescence" markers (Ibegbu, 2005).

3.11. The role of chromatin modifications in Alzheimer's disease: DNA methyltransferases (MTases) and Restriction endonucleases (REases) have traditionally used to protect microorganisms against foreign DNA. They are normally utilized as complementary components of restriction modification (RM) systems. Moreover, they recognize DNA sequences with 2-15 in nucleotide base length and methylate or cleave DNA (Steinberg, 2009). The genes of RM systems are attributable to the mobile genetic like as viruses, plasmids, integrons and transposons, since they have been regarded as genetic elements (Kobayashi, 2001). In view of the hypothesis of the pathogenic chromatin modification, microbes containing the pathogenic chromatin modifiers or their genes cause infection in their hosts that are vulnerable to the pathogenic chromatin modifiers. This process can contribute to the procedure of initiation and promotion of the disease. This hypothesis recommended that there is possibility for contribution of pathogenic chromatin modifiers in the DNA damage process that is found in AD. In the other words, chromatin modification from pathogenic chromatin modifiers in the brain has a vital role in the amyloid beta pathology and treatment (Kobayashi, 2001).

3.12. The roles of viral microRNAs in Alzheimer's disease: MicroRNAs (miRNA), as a type of small RNA, have an influential key role in regulating the biological pathways in both animals and plants. In this regard, miRNA-101 has been characterized as an inhibitor of invasion and migration of prostate cancer cell lines (Cao, 2010), which down regulates the amyloid precursor protein. This protein has an influence on the accumulation of the amyloid beta proteolytic products, which its relationship with AD has been shown in some studies (Vilardo, 2010). About 900 miRNA are known to be encoded in the human body by some viruses such as HCMV, and the human genome. At least 14 types of miRNA are encoded by human cytomegalovirus (HCMV).

4. CONCLUSION

There is ample evidence that support the role of infectious agents including viruses in the etiology of AD. Our general understanding of the impact of the infectious agents is expression proteins (pentapeptides or more) with obvious homology to β-amyloid protein and amyloid precursor protein. Another finding to emerge from the current study is the substantiate association of HSV-1 in subjects with APOE, HHV-6, CMV, EBV, BDV, Picorna and Influenza virus with AD. Some viruses including HSV-1 significantly affect on exacerbate AD pathology. They act via an effect on cellular pathway with interaction of the cell elements and cellular cascade within the host that causes triggering of AD. Cytokines and molecules associated with the viruses are released into the blood stream, which might have an effect on the microglial cells by crossing the blood-brain barrier. It must consider that viral interactions have triggered to certain susceptibility genes. Rationale behind this idea was that some form of synergy between the pathogen and genetic factors might have a vital role in the pathology of AD. Therefore, with the prevention and treatment of such infectious agents the sanitation authorities can decrease the risk of Alzheimer's disease. Beyond ensuring the strong correlation between viruses and AD which have been so far confirmed, more investigations will be needed in order to attain better insight into the exact cellular and molecular mechanisms by which infectious agents cause AD which may lead to novel approaches that can treat the disease.

Conflicts of interest: The authors declare that there is no conflict of interest in the current study.

Ethical standard statement: The research meets all applicable standards for the ethics

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