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Alzheimer's disease and infection: Do infectious agents contribute to progression of Alzheimer's disease?

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Abstract Infection with several important pathogens could constitute risk factors for cognitive impairment, dementia, and Alzheimer's disease (AD) in particular. This review summarizes the data related to infectious agents that appear to have a relationship with AD. Infections with herpes simplex virus type 1, picornavirus, Borna disease virus, *Chlamydia pneumoniae*, *Helicobacter pylori*, and spirochete were reported to contribute to the pathophysiology of AD or to cognitive changes. Based on these reports, it may be hypothesized that central nervous system or systemic infections may contribute to the pathogenesis or pathophysiology of AD, and chronic infection with several pathogens should be considered a risk factor for sporadic AD. If this hypothesis holds true, early intervention against infection may delay or even prevent the future development of AD.

Keywords: Alzheimer's disease; Dementia; Viral infection; Bacterial infection; Inflammation; Vascular risk factor; Vaccination

1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia in developed countries, and is the leading socioeconomic problem in healthcare [1,2]. Its etiology is recognized as multifactorial, with the possible inclusion of infectious agents. AD is generally considered a neurodegenerative disease [3], and may have a cerebrovascular disease (CVD) component, insofar as the risk factors for sporadic AD overlap with well-known vascular risk factors [4,5]. Sporadic AD, which is the most common form of dementia and which generally develops in late life, is thought to arise from multifactorial causes, as revealed in many epidemiological studies [4,5]. Even if these risk factors are taken into consideration, however, sporadic AD cannot fully be explained.

In the 1960s and 1970s, researchers observed elevated levels of antibodies to herpes simplex virus type 1 (HSV-1) in patients with psychiatric disorders [6,7]. On the basis of these results, Sequiera et al studied HSV-1 nucleic-acid sequences in the brain of demented and psychiatric patients [8], and found that the HSV-1 genome was present in brain samples of elderly patients with dementia. Some groups subsequently searched for a causal relationship between late-onset sporadic AD and viral infection, but many of them failed to show any association [9–11]. They investigated various kinds of viruses, including HSV-1 and HSV-2, measles virus, adenoviruses, cytomegalovirus (CMV), poliovirus, hepatitis B virus, and influenza virus A and B. Renvoize et al [12] and Renvoize and Hambling [13] measured serum antibody titers to CMV, adenovirus, chlamydia group B, *Coxiella burnettii*, HSV, influenza A and B, measles virus, and *Mycoplasma pneumoniae* in AD patients, and did not observe any association. These negative results may be attributable to the methodologies used, which may not have been sensitive enough to detect the viruses' genome. Indeed, other researchers provided a substantial body of evidence for the presence of HSV genomes in the brains or serum of AD patients, using the polymerase chain reaction (PCR) [14,15]. Previously, spirochetes were also investigated as a potential cause of AD [16,17]. More recently, two other bacteria, *Chlamydia pneumoniae* (*C. pneumoniae*) and *Helicobacter pylori* (*H. pylori*), were reported to have an association with the development of AD [18,19].

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Reports indicate that a few types of infectious agents, such as *C. pneumoniae* and spirochetes, can be detected in the brains of AD patients, often alongside senile plaques or neurofibrillary tangles (NFTs) [18,20], the characteristic brain pathology of AD patients. Moreover, the brains of AD patients are characterized not only by senile plaques and NFTs, but also by inflammatory responses and oxidative reactions [21,22]. There is evidence that aging contributes to inflammation in the brain [23], and it may be reasonable to hypothesize that infection with certain pathogens may play a role in the acceleration of this inflammatory response and increased oxidation. In addition, it was shown that once beta-amyloid (Aβ) plaques are formed, inflammation and oxidation recur [22], suggesting a vicious cycle in the pathogenesis of sporadic AD.

We review the relationship between AD and infectious species, and discuss the possibility of a causal effect of infection on cognitive impairment, using Bradford Hill's criteria. We also discuss the relationships between infection, CVD, and development of AD. If infections would contribute to the course of AD, this could have important implications for future prevention, and perhaps treatment, of AD.

2. Potential infectious agents

2.1. Viruses

2.1.1. Herpesviruses

2.1.1.1. Herpes simplex virus type 1

Herpes simplex virus type 1 (HSV-1) establishes a lifelong infection in the peripheral nervous system of most individuals after primary infection [24,25]. The infection is usually latent, but various nonspecific inflammations can trigger reactivation, such as herpes labialis. Mouse studies showed that HSV-1 can enter into the body via multiple routes, and can replicate without any neurological signs [26,27]. Herpes simplex virus type 1 can also infect the human central nervous system (CNS) latently [28].

The HSV group was investigated as a risk factor for dementia, and in the last two decades, many investigators found evidence of a relationship between HSV-1 and AD [8,14,15,25,29,30]. Sequiera et al studied HSV-1 nucleic-acid sequences of the brain in both HSV-1-inoculated mice and in three demented patients [8]. Herpes simplex virus nucleic acid was detected in mice until 24 weeks from the time of inoculation, whereas histological examination and virus isolation detected the HSV-1 only during the first 1 or 2 days. They also found that the HSV-1 genome existed in the brain samples of two demented patients and one schizophrenic elderly patient. Other groups investigated the relationship between dementia and HSV-1 in brain samples, using hybridization techniques, and dismissed HSV-1 as a potential agent associated with sporadic AD [9–11]. Renvoize et al used serum antibody titers to detect HSV in AD patients, and also failed to find a positive relationship between HSV-1 and AD [12,13]. On the other hand, many studies since the 1990s showed the existence of the HSV genome in the brains of AD patients and in normal elderly patients, using PCR amplification [14,15,25,29–32].

Animal studies found that latent infection with HSV-1 inoculation through nasal or corneal routes was associated with focal chronic inflammation and oxidative damage in the brain [27,33], and intracerebral inocula caused encephalitis and death in a few days [27]. These findings indicate that latent chronic asymptomatic infection with HSV-1 in the human brain might occur through the nasal route, and cause the chronic inflammatory and oxidative damage that is generally found in the AD brain. One study showed that Aβ deposits are present in mouse brains after HSV-1 infection [34]. That study also showed that the infection increased intracellular levels of Aβ in neuronal and glial cells of β-site amyloid precursor protein (APP)-cleaving enzyme (BACE-1; its cleavage pathway results in Aβ), and of nicastrin, a component of γ-secretase, in vitro. These results suggest a direct contribution of HSV-1 to senile plaques formation.

Although HSV-1 was found in both AD and normal aged brains [14,15,25,31,32], many groups postulate an association with AD, based on the following findings: 1) in acute HSV-1 encephalitis, infection targets particular regions, including the frontal and temporal cortices and hippocampus, which are also most prominently affected in AD [35]; 2) viral DNA was found in the same regions as those most affected in AD, and not in regions much less affected in AD, such as the occipital cortex [14,15]; and 3) HSV-1 DNA was detected in only a very small proportion of the brains [15] or cerebrospinal fluid (CSF) [25] in younger people, indicating that the virus can enter the brain when an individual becomes older, perhaps because of a decline in the immune system [25].

Previous negative results probably occurred because the methods used were not sensitive enough to detect virus genome. The PCR can detect very small quantities of HSV-1 DNA, and the positive results of recent studies mean that latent HSV-1 DNA is present in the brains of a high proportion of AD patients and of healthy elderly people. Odds ratios (ORs) of HSV-1 for AD are between 0.48 and 1.69 (mean OR ± SD, 1.19 ± 0.44) in the studies that were performed using PCR (Table 1). Because of the high detection rate of HSV-1 in age matched normal controls, the ORs were low in all studies. The *apolipoprotein E* ε4 (*APOE* ε4) allele frequency was higher among HSV-1-positive AD patients than HSV-1-negative AD patients in some studies [29,36]. Herpes simplex virus type 1 infection was identified as a risk factor for the development of AD in people expressing the *APOE* ε4 allele, although HSV-1 alone is not a risk factor for AD [29,37,38]. The OR of *APOE* ε4 for HSV-1-positive AD patients was 16.8 in one study [29], but again, this finding is not consistent among studies [31,38]. An interaction at a heparin sulfate proteoglycan receptor on the cell surface between HSV-1 and apolipoprotein E (apoE)