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Viral Hypothesis and Antiviral Treatment in Alzheimer's Disease

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Abstract

Purpose of Review—Viruses, particularly herpes simplex virus (HSV), may be a cause of Alzheimer's disease (AD). The evidence supporting the viral hypothesis suggests that antiviral treatment trials, which have not been conducted, are warranted.

Recent Findings—HSV1 (oral herpes) and HSV2 (genital herpes) can trigger amyloid aggregation, and their DNA is common in amyloid plaques. HSV1 reactivation is associated with tau hyperphosphorylation and possibly tau propagation. Anti-HSV drugs reduce Aβ and p-tau accumulation in infected mouse brains. Clinically, after the initial oral infection, herpes simplex virus-1 (HSV1) becomes latent in the trigeminal ganglion and recurrent reactivation may produce neuronal damage and AD pathology. Clinical studies show cognitive impairment in HSV seropositive patients, and antiviral drugs show strong efficacy against HSV.

Summary—An antiviral treatment trial in AD is clearly warranted. A phase II treatment trial with valacyclovir, an anti-HSV drug, recently began with evaluation of clinical and biomarker outcomes.

Keywords

Alzheimer's disease; Viral hypothesis; Dementia; Amyloid; Tau; Antiviral treatment

Introduction

Some viruses are known to cause neurodegenerative disorders. Early infection with measles can lead, years later, to subacute sclerosing panencephalitis with co-localization of the measles virus genome with neurofibrillary tangles (NFT) in nerve cells [1, 2]. Tangles in substantia nigra cells typical of post-encephalitic Parkinson's disease reflect an initial viral trigger, and HIV infection leads to abnormal tau protein formation [2]. The long-standing viral etiology hypothesis of Alzheimer's disease (AD), which originated in the 1980s, posits

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Compliance with Ethical Standards

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Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

that viruses in the brain, primarily HSV1 (causes oral herpes) and to a lesser extent HSV2 (causes genital herpes), may be etiologic or contribute to the pathology of AD [3, 4]. Herpes viruses are large, double-stranded DNA viruses well-adapted to establish lifelong infection, rarely cause death, and spread readily between humans [5].

In a 2016 editorial, 31 senior scientists and clinicians pointed out that the scientific evidence strongly suggests that microbes may be a major cause of dementia, including AD [6••]. The review identified HSV1 as the most likely culprit and suggested an antiviral treatment trial to potentially slow or arrest disease progression in AD.

Herpes Simplex Virus Entry into the Brain

Seven separate groups have detected HSV1 in AD brains at higher rates than in control brains, and HSV1 DNA co-localizes strongly with amyloid plaques in AD brains but not in normal brains [6••, 7]. Features of AD pathology are transmissible by inoculation in mice and primates; a virus, possibly HSV1, may be involved [6••, 8, 9]. HSV1 proteins are present in hippocampal neurons of mice infected intraperitoneally with HSV1, indicating that blood-borne transmission may occur with HSV1 and HSV2 and account for the 10% of cases of herpes simplex encephalitis (HSE) found to be caused by HSV2 [10]. HSV1 and HSV2 look essentially identical under the microscope, share nearly all of their DNA, and have similar effects on AD pathology in cell culture models [1, 2].

The trigeminal ganglion is the primary reservoir for HSV1 during latency. In 147 autopsies, HSV1 DNAwas identified in the trigeminal ganglion in 90% of patients diagnosed antemortem with clinical AD [11]. Reactivation of the latent HSV1 virus in the trigeminal ganglion, which can occur decades after the original infection, can be anterograde with transport of viral particles to produce orofacial lesions, or retrograde with axonal transport of HSV1 particles to infiltrate the locus coeruleus and then progress to the temporal lobe, particularly the hippocampus and entorhinal cortex [12]. In HSV seropositive patients, viral DNA was detected from almost all combined postmortem tissue samples of trigeminal and olfactory ganglia [13]. Dendritic nerve terminals of olfactory receptor neurons are directly exposed, and macromolecules can enter these neurons and be transported trans-synaptically; in animal studies, HSV can use this mechanism to invade the brain via the olfactory pathway [14–16].

Virus Reactivation

Genetic factors can increase the risk of developing HSV infections. Defects in genes of the Toll-like receptor 3 (TLR3) are associated with susceptibility to HSE, and rare missense mutations in TLR3 (p.Leu297Val) and (p.Leu199Phe) have been associated with varicella zoster virus encephalitis [17]. A Fas gene polymorphism can influence herpes simplex virus type 2 infection in South African women, cell death pathway genes can predispose to HSV2 infection, and susceptibility genes are enriched among genes of the HSV1/host interactome in psychiatric and neurological disorders but without any robust specific gene effects [18–20]. HSV1 viral DNA enters nucleosomes in neurons of host cells and can become latent. HSV1 replicates in the CNS and can produce local neuronal damage, “drop by drop,” over

time and eventually lead to neurodegeneration and AD pathology [1, 6••]. Stress, decline in immune function, and increased blood-brain barrier breakdown with age may amplify this effect [1]. Asymptomatic virus shedding, or "subclinical reactivation," occurs in essentially all people infected with herpes simplex virus [5, 21]. In CSF, HSV can be identified by PCR in patients with HSE but was found in only 6% of all HSV seropositive cases among 112 patients referred for a variety of acute CNS symptoms or disorders, suggesting that examining CSF for HSV directly may not be a successful diagnostic strategy [22].

Herpes Simplex Encephalitis (HSE)

HSE is a severe illness that occurs in 2–4 per 500,000 people [23]. HSV causes HSE (causative agent HSV1 in 90% of cases; HSV2 in 10% of cases) in which the virus infiltrates limbic structures, particularly the hippocampus and frontal lobes, and memory loss, cognitive deficits, mood and personality changes occur with symptoms very similar to those in AD [1]. The long-term sequelae of HSE in adults include anterograde memory loss, deficits in working memory and visual object recognition, anosmia, and dysphasia [24, 25]. After HSE, long-term anatomic and functional damage is confined to the limbic system, particularly the hippocampus. The majority of HSE cases occur in people over 50, suggesting that blood-brain barrier disruption supports viral entry. Antiviral treatment with acyclovir or valacyclovir is effective in reducing mortality and severity of cognitive deficits but no placebo-controlled antiviral treatment trial has been conducted in HSE, a rare condition [26].

Inflammation

In HSE, IgG and IgM increase in the initial stages in serum and CSF, but over time, antibody levels are less consistent [27]. In 270 AD patients and 270 controls in which plasma had been sampled 6.6 years earlier, presence of anti-HSV IgG antibodies was associated with AD (OR 2.25, $p = 0.02$) [28•]. In another series from the same Swedish group, 3432 older adults were followed for 11.3 years. Anti-HSV IgM, but not anti-HSV IgG, was associated with incident AD that occurred in 245 cases (HR 1.96, $p = 0.012$) [29•]. IgG and IgM levels are the end-result of both old and new infections and can change with antiviral treatment; they do not correlate with drug side effects [1, 30]. In 588 patients with schizophrenia, there was an additive effect of C-reactive protein (CRP) and HSV1 seropositivity with odds of 2.35 to have an RBANS score ≤ 60 (neuropsychological test battery; lower scores indicate greater impairment) compared to HSV1 seronegative individuals without elevated CRP [31]. However, peripheral inflammatory markers like CRP are non-specific and can change due to many factors.

HSV Effects on Amyloid Pathology

In rodents with HSV-induced infection, spatial memory is impaired in the Morris water maze, which is analogous to the visuospatial memory tests being impaired in AD [14]. Amyloid plaques and neurofibrillary tangles are the pathological features of AD. HSV1 infection of neuronal and glial cells leads to increase in intracellular levels of amyloid-beta protein (Aβ), a decrease in amyloid precursor protein (APP), and phosphorylation of tau

protein, the main component of neurofibrillary tangles in AD [6••]. HSV1 DNA is localized in amyloid plaques in AD and HSV1 binding proteins are increased by 11- to 15-fold in amyloid plaques and neurofibrillary tangles [32]. HSV1 binds to plaque or tangle components involved in apoptosis, DNA transcription, translation initiation, protein chaperoning, the ubiquitin/proteasome system, and the immune network [32]. The virus deletes mitochondrial DNA and interferes with key proteins related to APP processing and signaling, β-amyloid processing, microtubule stability, and tau phosphorylation [33]. HSV2 has effects that are similar to HSV1 on amyloid [34].

APP interacts with HSV1 capsid proteins to allow the migration of new viral particles inside infected cells [35]. In cultured neuronal cells, HSV1 induces APP cleavage with production of several APP fragments including $A\beta_{42}$ [36]. HSV1 causes $A\beta_{40}$ and $A\beta_{42}$ accumulation in human neuroblastoma and glioblastoma cells in vitro, but in brains of mice infected with HSV1 only, an increase in $A\beta_{42}$ is observed, which is similar to neuropathological findings in AD [33]. HSV1 induces a significant accumulation of $A\beta_{42}$ inside neurons, and this effect depends on Ca++ signaling activation [37, 38]. HSV1 binding to neuronal membrane leads to hyperexcitability and it increases Ca++ entry into the cell that can trigger cell death [14]. In an AD autopsy study, 90% of amyloid plaques contained HSV1 DNA and 72% of HSV1 DNA was plaque-associated; the comparison group of aged normal brains contained less plaques, and only 24% of HSV1 DNA was plaque-associated ($p < 0.001$) [7]. These findings suggest a strong association between HSV1 and amyloid plaques in AD brains and a much weaker association in normal brains, supporting the link between HSV1 and amyloid in AD.

HSV and Tau Propagation

HSV1 causes tau phosphorylation at several sites, including serine 202, threonine 212, serine 214, serine 396, and serine 404, and it induces glycogen synthase kinase 3β and protein kinase A, enzymes that cause phosphorylation at these sites [39]. CSF phospho-tau (P-tau) is increased in both AD and HSV-1 encephalitis [40]. HSV kinases can phosphorylate human proteins, and human kinases can phosphorylate HSV proteins, illustrating a cross-species kinase “promiscuity” and interchange of enzyme/substrate interactions that may be important for AD [14]. In the brains of 45 patients with dementia and 12 age-matched controls, morphometric data from 1,328,743 microscopic fields suggested spread of lesions with neuron-to-neuron spread of an etiological trigger [14]. Neuronophagia by microglia has been shown in dementia, and this is a marker of cerebral viral infection such as HSE [14]. There is exosomic secretion of HSV-1-infected cells’ L-particles. Cell-to-cell passage of microRNAs of HSV is supported by amino acid homology between human p-tau and VP22, a key target for phosphorylation by HSV serine/ threonine-protein kinase UL13. Therefore, HSV1 may underlie neuron-to-neuron propagation of tau protein and AD changes in the brain [1, 2, 41, 42].

Epidemiology of Herpes Simplex Virus (HSV) in AD

In the USA, up to 80% of older adults have had HSV infection during their lifetimes with persisting serum antibodies [23]. In a community study, anti-HSV1 IgM positivity, reflecting reactivated infection, was associated with AD-like cognitive dysfunction [43]. HSV1

reactivation, assessed by the anti- HSV avidity index, occurs in prodromal AD and correlates with cognitive symptoms [44]. Elevated HSV1 serum anti-body titers may be more frequent in AD and mild cognitive impairment (MCI) than healthy controls [45]. Odds ratios for the association between CNS infection with HSV1 and AD range from 1 to 3 across studies [1, 43]. In one report, HSV1 and AD were not associated but there was a modest association between cytomegalovirus (CMV) infection and AD based on IgG antibody levels [46]. However, latent CMV resides mainly in lymphocytes, not neurons, and IgG levels are affected by many factors.

HSV Seropositivity and Cognitive Impairment

In 240 adult controls, HSV1 seropositivity was associated with a worse neuropsychological test battery (RBANS) score and HSV1 seropositivity was associated with an 18-fold increased odds of having severe impairment in delayed memory [47]. In a Finnish study of 383 home-dwelling patients with cardiovascular disease, seropositivity for HSV1, HSV2, and CMV was associated with lower Mini Mental State Exam (MMSE) scores and with worsening in MMSE and Clinical Dementia Rating (CDR) scores during 1 year of follow-up. With 0 to 1 viral seropositivities as reference, hazard ratios for 2 and 3 viral seropositivities were 1.8 (95% CI 0.9, 3.6) and 2.3 (95%CI 1.1, 5.0), respectively [48]. In an African-American cohort (680 patients with schizophrenia, 889 healthy relatives, 283 healthy controls), the composite score of 9 cognitive domains was lower with exposure to CMV or HSV1 regardless of case/relative/control status ($p = 1.09 \times 10^{-5}$ and 0.01, respectively), with stronger associations among those with impaired cognitive scores and exposure to multiple herpes viruses ($\beta = -0.25$, $p = 7.28 \times 10^{-10}$) [49].

There are similar findings in psychotic disorders. In 229 patients with schizophrenia, IgG positivity for HSV1, but not CMV, EBV, or HZV, independently predicted cognitive dysfunction, mainly in a test of immediate memory after controlling for age and education (Cohen's $d = 0.45$) [50]. In 1308 patients in the NIMH-supported CATIE trial in schizophrenia, neurocognitive summary score was associated with antibodies to HSV1 but not to HSV2, CMV, or *Toxoplasma gondii* ($t = 2.60$, $p = .009$) [51]. The domains that showed associations with HSV1 seropositivity included verbal memory, vigilance, and processing speed [4]. In 117 patients with bipolar disorder compared to 100 controls, HSV1 seropositivity was strongly associated with worse RBANS neuropsychological score ($p < 0.001$), mainly in immediate memory [52].

The associations between prior exposure to HSV, particularly HSV1, and cognitive impairment appear to be significant and reproducible, using different cognitive test batteries and after controlling for key variables that include age, sex, socioeconomic status, and exposure to other herpes viruses. The associations are detectable in healthy individuals, older individuals with cardiovascular disease, and patients with psychotic disorders.

Risk Factors

In HSV seropositive patients, apolipoprotein E ε4 genotype, which is a well-established risk factor for AD, may be associated with increased HSV1 and HSV2 recurrence, and having

the ε4 allele may be associated with increased viral load in the brain [1, 53]. Viral spreading into the brains of apolipoprotein E knockout mice was lower than in wild-type mice with a positive correlation between apolipoprotein E expression and HSV1 DNA concentration in the CNS [10]. During acute infection with HSV1, apolipoprotein E ε4 was more efficient than apolipoprotein E ε3 in promoting viral colonization of the brain [54]. In AD, HSV1 seropositivity is more common in apolipoprotein E ε4 carriers than apolipoprotein E ε4 negative patients [6••, 10, 32].

Some Findings Do Not Support the Viral Hypothesis of AD

A strong linear association between HSV1-specific antibodies and AD has not been established, partly because of the high rate of HSV seropositivity in older adults [6••]. HSV-1- specific IgG and IgM levels in blood are increased in some but not all studies of AD; this may be because some immunoglobin levels can be altered by both old and new viral infections and other factors [1, 43, 44]. A large portion of the non-AD elderly population shows HSV1 DNA in brain autopsies, which is likely to be related to the high rate of HSV1 infection in older adults. Conversely, some HSV1 carriers do not develop AD [55]. Therefore, if herpes simplex viruses contribute to AD etiology and pathogenesis, it is likely that only some patients who have been exposed to HSV will develop AD pathology. Patients who develop AD may have latent infection with a “high phenotypic reactivator strain” of HSV with long latency in the brain and the potential for reactivation after many years [14]. Further, people can be infected but not affected, such that “controls,” even if infected by HSV, are asymptomatic [1]. These findings indicate that HSV cannot be the sole cause of AD, but the bulk of the evidence shows that HSV infection is likely to be important in the etiology of AD and may contribute to the cognitive deficits and neuropathology of AD.

Bradford-Hill Criteria

The association between HSV1 and cognitive impairment meets several Bradford-Hill criteria (guidelines for causal relationship between putative cause and effect): impairment is consistent, plausible, has a moderate effect size, is not attributable to obvious confounding factors, and a temporal relationship between HSV exposure and cognitive deficits is likely in patients with cardiovascular disease and in healthy adults [48, 56]. However, the “biological gradient” between exposure dose and dysfunction severity cannot be tested accurately because HSV1 antibody titers do not conclusively reflect severity or duration of exposure and direct testing for HSV by PCR has a low yield of 6% in the CSF of patients referred with CNS symptoms/disorders [22]. While detection of antibodies against HSV1 surface protein gG-1 is 100% specific and 98% sensitive for exposure to HSV1, repeated reactivation leads to lifelong elevation of viral titers that do not indicate duration or timing of HSV exposure [11, 57, 58].

Treatment

Current treatments for AD have limited efficacy [25]. There is a compelling need to develop effective treatments for this debilitating disease that will more than double in prevalence by

2050. Cholinesterase inhibitors and memantine are the only FDA-approved medications for AD. Their efficacy is small in magnitude, and they do not alter the course of the disease. All other therapeutic strategies have failed in a large number of treatment trials, including antiamyloid treatments like solanezumab. In fact, one study based on the amyloid hypothesis showed worsening of function on the gamma-secretase inhibitor semagacestat compared to placebo [58].

Antiviral Drug Effects

In a cell-culture model, the anti-HSV1 antiviral agents acyclovir, penciclovir, and foscarnet reduced HSV1 particles and Aβ and P-tau accumulation [59]. Antiviral-induced decrease in Aβ correlated with reduced number of viruses. Anti-HSV drugs reduce both Aβ and P-tau accumulation in brains of HSV-infected, asymptomatic mice [6••, 60].

Mechanism of Action

Valacyclovir is the most widely used drug to treat peripheral HSV1 and HSV2 infections, and other antiviral drugs effective against herpes viruses are similar to valacyclovir in their molecular structure and mechanism of action. Valacyclovir, a pro-drug of acyclovir, is converted by viral thymidine kinase into its monophosphate (acyclo-GMP) and triphosphate (acyclo-GTP) forms. Acyclo-GTP is a potent inhibitor of viral DNA polymerase with 100 times higher affinity to viral than cellular polymerase [61]. Viral enzymes cannot remove acyclo-GTP from the chain, which results in inhibition of further DNA polymerase activity and consequent chain termination. Its monophosphate form, acyclo-GMP, also incorporates into viral DNA, leading to chain termination [1, 60]. Therefore, valacyclovir leads to death of infected cells but it does not affect the DNA of non-infected cells; hence, its side effect profile is benign. In patients with clinical HSV1 and HSV2 infection, sustained valacyclovir use for up to 7 years has been shown to maintain HSV suppression [59, 62, 63]. Valacyclovir's sustained action suggests that it may be both symptomatic in the short-term and disease-modifying in the long-term if it is shown to be effective in AD.

Antiviral Treatment in Neurological and Psychiatric Disorders

Valacyclovir has been tested in multiple sclerosis (MS) with equivocal results. MS lesion size on brain MRI scan and clinical disability were the outcome measures; cognition was not assessed in the two MS trials [24, 64]. In a randomized, double-blind, placebo-controlled, 18-week trial in 24 patients with schizophrenia with positive HSV1 titers, valacyclovir at a dose of 3 g/day was superior to placebo with effect sizes of 0.79, 0.97, and 1.14 for tests of working memory, verbal memory, and visual object memory, respectively, from the computerized Penn neuropsychological battery [65]. These results are promising for the treatment of schizophrenia, specifically in individuals with prior exposure to HSV infection. In an open-label study of 43 of 61 patients with chronic fatigue syndrome who received valgancyclovir, an antiviral drug closely related to valacyclovir that is used to treat CMV, subjective cognitive improvement of at least 30% sustained for 12 months was reported [66]. Valacyclovir also improved cognition in anecdotal reports of patients with HSE, but there has been no randomized clinical trial in this rare condition [5, 26].

Valacyclovir Trial in AD

The bulk of the evidence suggests that HSV1 and HSV2 may contribute to AD neuropathology. Valacyclovir is a pro-drug of acyclovir and is the most widely used generic antiviral drug with over 15 years of worldwide use and an excellent safety profile. Valacyclovir is highly effective against HSV1 and HSV2, moderately effective against varicella zoster, and virtually ineffective against Epstein-Barr virus and cytomegalovirus (CMV) [30]. It is approved by the FDA for the treatment of HSV1, HSV2, varicella zoster (shingles), and chickenpox [30]. A new trial of valacyclovir treatment in AD is the first-ever antiviral treatment trial in AD.

Risks with Valacyclovir Treatment

Valacyclovir has a generally benign safety profile. Hallucinations, delirium, and seizures occur in < 1% of patients taking valacyclovir in oral doses of 2–4 g daily and manifest only in patients with renal failure [61, 63, 67]. There is good CNS penetration of valacyclovir with a largely linear relationship between oral dose and CSF levels in healthy controls, MS, and HSE, with long-term persistence of these CSF levels for at least 6 months with continuing valacyclovir treatment in MS [68–73].

Dose

The recommended oral dose of valacyclovir for peripheral acute HSV infections is 1 to 3 g daily, and bioavailability is 54% [4]. For long-term HSV suppression, the dose is 1 g daily [30]. The difficulty in obtaining efficacy for any drug in AD suggests that a higher flexible dose range may be advisable; the flexible dose range of 2 to 4 g daily will be used in the clinical trial. The dose of 3 g daily is at the upper end of approved doses for peripheral HSV infection and was effective in the schizophrenia pilot trial [65].

In the trial, the aim is to evaluate valacyclovir, a repurposed generic antiviral drug, as a treatment for AD [25]. This is a phase II, proof of concept, randomized, double-blind, placebo-controlled, 18-month treatment trial of 130 patients (65 valacyclovir, 65 placebo) with mild AD (MMSE range 20–28) who test positive for antibodies to HSV1 or HSV2. Valacyclovir dose will be 2–4 g daily. The dose range is safe, increases the chance of finding efficacy, and is known to lead to CNS penetration with high CSF levels over an extended period in patients with multiple sclerosis, HSE, and healthy controls [68–70].

Hypotheses are that patients treated with valacyclovir will show smaller decline than patients treated with placebo on the Alzheimer's Disease Assessment Scale-Cognition 11-item scale (ADAS-Cog11; cognitive measure; 0 to 78 weeks) and the Alzheimer's Disease Cooperative Study-Activities of Daily Living scale (ADCS-ADL; function measure; 0 to 78 weeks). The biomarker hypothesis is that patients treated with valacyclovir will show less accumulation than patients on placebo in PET amyloid scans (F-Florbetapir, 0 to 78 weeks) by evaluating the sum of six ROIs (cerebellar reference) that show increased uptake in AD: medial orbital frontal, anterior cingulate, parietal, temporal, posterior cingulate, precuneus [59]. Additional measures examined will be apolipoprotein E ε4 genotype as a potential moderator of outcome, changes in serum antibody levels to HSV1 and HSV2 (plus sub-analyses of IgG,

IgM), MRI “signature” in AD of regional cortical thinning and whole brain cortical thinning, and CSF acyclovir levels to examine plasma/CSF acyclovir correlations [74]. CSF studies will be optional and approximately one-third of the sample is expected to agree to lumbar puncture. If either an efficacy measure or biomarker indicates evidence of efficacy or biomarker change, respectively, there is likely to be justification for moving to a phase III trial.

Conclusions

There is considerable basic science and epidemiological evidence that infectious agents may be contributing to the neuropathology and clinical manifestations of AD, and that HSV1 is the most likely culprit while HSV2 may also contribute. The viral hypothesis of AD has been in the literature for three decades and the evidence supporting this hypothesis has accumulated steadily over time. While HSV is unlikely to be the sole cause of AD, an antiviral treatment clearly needs to be evaluated in AD, particularly in light of the limited effects of existing treatments and the failure of all new treatments that have been tested in clinical trials in patients with AD during the last two decades.

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