Page 652 to 660

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# Alzheimer's Disease: Questions Raised by a Herpes Virus Origin

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## Abstract

As in the case of other CNS infectious agents claimed to cause Alzheimer's disease [AD], the theory that Herpes Simplex Virus or any other herpes virus causes AD is still controversial. In their 2013 review, Mawanda and Wallace's *Can Infections Cause Alzheimer's Disease* [1] gave seven annotated references as to why HSV-1 "remains questionable" as a cause for Alzheimer's. Some say that Herpes simplex virus type 1 in conjunction with APOE-epsilon 4 allele is a strong risk factor for AD, though either of these features alone do not increase the risk for AD. It is claimed that people who have symptoms of late onset Alzheimer's disease (AD) and have one or more APOE-ε4 gene copies are more likely to have AD. However, APOE-ε4 is not diagnostic of AD and should not be used to screen people or their family members. Furthermore, many of those who have ε4 alleles will never develop AD. And even in symptomatic people, only about 60% of those with late onset AD will have APOE-ε4 alleles [2, 3]. Not only is the APOE gene not a clinical diagnosis, but just as importantly, "negative" results do not confer later protection. Beyond APOE, there are at least 20 other genetic factors which have been shown to have a small but significant role in determining Alzheimer risk [4]. And true understanding of genetic test results also requires attention to potential inaccurate results. For example, APOE-ε4 alleles themselves are known to show a distinct increase in tuberculosis [5]. Before widespread institution of anti-herpetics on the general population, this is an area which requires further research.

***Keywords:*** *Alzheimer's disease; Etiology of Alzheimer's disease; Infectious Alzheimer's disease; Questions Raised by a Herpes Virus Origin of Alzheimer's disease; Herpes Simplex Virus; The use of anti-herpetics in Alzheimer's disease*

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## Introduction

In the case of Herpes Simplex Virus type 1 — an estimated 80 percent of the U.S. population has HSV-1. To Alzheimer's specialist Jagan Pillae of the Cleveland Clinic, the connection between HSV-1 and Alzheimer's is still murky and "T*he research does not say, nor does it tell us if herpes simplex 1 virus caused Alzheimer's. The studies show that for some as-yet unclear reason, immune changes related to herpes simplex 1 appear to be more common in older individuals (meaning older than age 60) with Alzheimer's. The research does not say, nor does it tell*

*us, if the herpes simplex 1 virus caused Alzheimer's. It could be that immune changes related to Alzheimer's disease simply cause more reactivations of the virus"* [6]. This obviously could be due to aging or an underlying chronic immunosuppressive infection. Contini., *et al.* [7] investigated an association between various infectious agents and AD, "*but none of these has been accepted as either etiological for disease development, or worsening of neuropathology.*" Although "interesting perspectives" came from Herpes simplex virus type1 (HSV-1) in subjects expressing APOE ε4 allele [8,9] , –measles virus, adenovirus, lentiviruses, hepatitis C, cytomegalovirus and several other viruses, were also initially considered for AD but later discarded [10,11].

Nimgaonkar., *et al*. [12], in a 2016 study originating at the University of Pittsburgh and published in the Journal *Alzheimer's Disease* and *Associated Disorders*, maintained that HSV-1, often associated with cold sores - and which an estimated 3.7 billion people under the age of 50 have worldwide –is not associated nor linked to greater temporal cognitive decline. In addition, Greg Cole, the associate director of the Geriatric Research and Clinical Center at the UCLA Alzheimer Disease Research Center in Los Angeles, also isn't totally convinced: "*More than 90 percent of the population has antibodies to herpes, and they are not all destined to develop Alzheimer's disease*," he said. [https://consumer.healthday.com/cognitive-health-information-26/alzheimer-s-news-20/studies-link-cold-sore-virus-to-alzheimer-s-risk-692988.html] Clinically, according to the NIH (National Institutes of Health), Herpes Simplex encephalopathy is a rare disorder, classified as a 'rare diseases'. [https://rarediseases.info.nih.gov/diseases/6649/herpes-simplex-encephalitis]

## Shaky Consensus

There are several more specific reasons that the role of HSV-1 in the causation of AD could be considered as remaining "*questionable*". Several studies of post-mortem brain tissues found no evidence linking HSV-1 to AD [13-19]. For example, Taylor *et al*. [14] used *in situ* hybridization to analyze postmortem brain samples (55 from 8 patients with AD and 57 from 9 non-neurologic control patients), as well as samples from HSV-1-infected mice. With this technique, none of the samples revealed detectable levels HSV-1 DNA. In another in situ hybridization study, Roberts *et al*. [15] examined postmortem brain specimens from 25 patients with AD and 32 controls, but none hybridized to HSV-1 DNA probes. Similarly, HSV-1 DNA was not detected by Southern blotting in any postmortem brain tissue samples or peripheral blood cells obtained from 5 patients with AD and 5 normal controls [18]. These negative findings, however, could be due, in part, to differences in methodology because *in situ* hybridization and Southern blotting are less sensitive than PCR in detecting DNA. Consistently, the majority of studies reporting positive findings used PCR. Nevertheless, even in the case of PCR, most PCR-based studies showed no significant difference in the frequency of AD versus control brain tissue samples that contain HSV-1 DNA [20-27]. Several serology-based studies also found no evidence to link HSV-1 infection to AD [28-30]. For example, Renvoize *et al.* [29] analyzed serum from 33 patients with clinical diagnosis of AD and 28 controls suffering from psychiatric disorders but without evidence of comorbid dementia. They found that serum from the 2 groups did not differ significantly in the levels of antibody titers to various viral pathogens, including HSV-1, but this result is not surprising given the high prevalence of HSV-1 among older adults. Yet Ounanian *et al.* [28] actually found that controls, rather than patients with AD, showed higher levels of anti-HSV-1 antibody titers. Thus, lack of consistency leaves studies linking HSV-1 to the causation of AD inconclusive. Also, in Potgieter's review of dormant blood microbiomes in chronic, inflammatory diseases [31]; in Figure 5 on page 579, appear coccus-shaped bacteria associated with Alzheimer's (AD), with nothing to do with Herpes Simplex type 1.

## Murky Methodology

Kary Mullis, the inventor of that PCR, and as a result a Nobel Laureate, was very clear regarding what constitutes PCR's valid uses. Mullis said that such tests cannot detect free, infectious viruses at all; they can only detect proteins that researchers believe, in some cases wrongly, are unique to the virus being tested for. The tests can detect genetic segments of viruses, but not viruses themselves [32]. In her study *Life-Threatening Herpes Simplex Virus Infections in the Normal and Immunocompromised Host*, Birgit Sköldenberg, an Associate Professor of Infectious Diseases at the Karolinska Institute in Stockholm pointed out that other diseases can be confused with Herpes simplex encephalitis (HSE) "such as tuberculosis, brain abscess or tumor, and other viral infections"[33]. These are all in the differential diagnosis of Herpes simplex encephalitis, and therefore should be considered. Certainly this was the case in a September, 2016 case published by Oxford University press on behalf of the *Infectious diseases Society of America* (IDSA). The publication was entitled

the "*Delayed Diagnosis of Tuberculous Meningitis Misdiagnosed as Herpes Simplex Virus- 1 Encephalitis with the FilmArray Syndromic Polymerase Chain Reaction Panel*" [34]. In October 2015, the FDA cleared the first multiplex, meningitis/encephalitis (ME) PCR panel (FilmArray ME panel; BioFire Diagnostics LLC, Salt Lake City, UT) for the diagnosis of most common infectious etiologies of acute central nervous system (CNS) infections. This fully automated, sample-to-answer, multiplex polymerase chain reaction (PCR) assay required <2 minutes of hands-on time, and in 1 hour it tests for 14 ME pathogens, including bacteria, fungi, and viruses [35]. Not included in the FilmArray Meningitis/Encephalitis (ME) Panel, however, was any means of detecting another prominent ME agent, *M. tuberculosis*. So below is a classic illustration of what you don't look for, you don't find.

One of the many patients to be subjected to this particular PCR panel was a 75-year-old Vietnamese man, who immigrated to California more than 40 years ago, and not unlike Auguste Deter, Alzheimer's first patient, presented with confusion, disorientation to time and place, but with no focal neurologic deficits. In this case, a spinal tap was negative for Gram and acid-fast stains but cerebrospinal fluid tested with the FilmArray ME PCR panel was positive for HSV-1, prompting the initiation of intravenous anti-viral acyclovir therapy for HSV encephalitis. It was because of failure, and worsening of this patient's condition while on such anti-viral treatment that an Infectious Diseases (ID) consult was requested to expand the diagnostic workup for chronic meningitis. Per the ID recommendations, additional CSF testing by real-time PCR for HSV-1/HSV-2 (artus HSV-1/2 QS-RGQ Kit; QIAGEN, Germantown, MD), VZV, and CMV (also from QIAGEN), and cryptococcal antigen detection by lateral flow immunochromatography (IMMY, Norman, OK) were done. All yielded negative results.

On hospital day 7, *Mycobacterium tuberculosis* nucleic acid testing on a CSF sample, using a laboratory-developed PCR assay [36], was positive and tuberculosis therapy with first-line drugs (isoniazid, rifampin, pyrazinamide, and ethambutol) and dexamethasone was initiated. Cerebrospinal fluid cultured in liquid medium (MGIT960 system; Becton Dickinson, Franklin Lakes, NJ) turned positive for *M tuberculosis* after 13 days. Phenotypic susceptibility testing with first-line drugs demonstrated a pan-susceptible isolate. Unfortunately, in large part due to the initial delay in proper diagnosis, over the following weeks, despite aggressive clinical management, the patient did not have meaningful neurologic recovery and eventually required a tracheostomy and gastric feeding tube for transition to a rehabilitation ward, where he continued on tubercular therapy with severe neurological deficit. So in this study, we have a case of tuberculous meningitis leading to severe neurological sequelae, in an immunocompromised patient whose diagnosis was delayed due to a false-positive Herpes Simplex virus (HSV)-1 result with the FilmArray ME panel PCR.

More importantly, no matter how sensitive and sophisticated today's diagnostic tests and next-generation PCRs are, they still do not address the concerns of Alzheimer's specialist Jagan Pillae of the Cleveland Clinic, who feels the connection between HSV-1 and Alzheimer's is still cloudy and that it could be that immune changes related to Alzheimer's disease simply cause more reactivations of the virus [6]. And, it is not inconceivable that such immune changes come as a result of an immunosuppressive primary infection, to this point, undetected.

## Persistent Inaccuracies

In the face of a 2006 study by Helmer [37] which found that anti-herpetic medicines such as acyclovir were "not significant" for lessening dementia such as found in Alzheimer's; Tzeng *et al*. in a 2018 retrospective Taiwanese study not only suggested that patients with HSV infection "may have" a 2.56-fold increased risk of developing dementia, but that the usage of anti-herpetic medications was associated with a decreased risk of dementia [38]. The latter study seemed to suggest the off-label use of anti-herpetics for Alzheimer's. When she worked on the original anti-herpetic for HSV, Gertrude Elion felt she had determined exactly how and why it worked. To Elion, acyclovir, marketed as Zovirax®, interfered with the replication process of the herpesvirus –and only the herpesvirus –proving that drugs can be selective. That is until a Polish study proved this wrong. And so while Western literature remained silent about acyclovir as having anything but anti-viral activity, Kruszewska, in Poland, found that acyclovir actually had activity against *Pseudomonas aeruginosa* and *E. coli* –two out of only 4 bacteria used in this study that acyclovir was tested as having activity against [39]. Yet, for reasons unknown, no other bacterial pathogens other than the ones in this limited Polish study were ever tested for against the activity of this prototype anti-herpetic –either before Kruszewska or since [40].

## Virus or Red Herring?

Probably one of the leading advocates for the theory that Herpes Simplex Virus type 1 in many cases causes Alzheimer's is Professor Ruth Itzhaki, Professor Emeritus of Molecular Neurobiology at the University of Manchester. In an article posted on October 19, 2018 [https://theconversation.com/alzheimers-disease-mounting-evidence-that-herpes-virus-is-a-cause-104943] Professor Itzhaki mentioned: "*It's important to note that all studies, including our own, only show an association between the herpes virus and Alzheimer's – they don't prove that the virus is an actual cause. Probably the only way to prove that a microbe is a cause of a disease is to show that an occurrence of the disease is greatly reduced either by targeting the microbe with a specific anti-microbial agent or by specific vaccination against the microbe*."

But in another recent interview Dr. Itzhaki asserted "HSV-1 could account for 50 percent or more of Alzheimer's disease cases" [41]. Itzhaki previously had found that for those that carry a copy of the APOE-ε4 gene, the gene that is most commonly associated with Alzheimer's, that this gene can reactivate the Herpes Simplex 1 in the brain [8]. But seven years later Farivar, in the Journal of Applied Sciences, found the same APOE-ε4 genotype significantly more elevated in TB patients as opposed to controls [5]. Itzhaki went on to say that "*The likelihood of developing Alzheimer's disease is 12 times greater for APOE-ε4 carriers who have HSV-1 in the brain than for those with neither factor*". Yet what is left out here is that according to the *National Institutes of Health* (NIH) herpes encephalitis is a rare disease to begin with. Also with APOE-ε4, it's not just about herpes virus. It is well known that HIV causes a form of AIDS dementia which happens to be more common in carriers of APOE-ε4. Just as importantly, APOE-ε4 alleles themselves are known to show a distinct increase in mycobacterial disease, the leading cause of AIDS infectious death.

In still another October, 2018 review, this time entitled *Corroboration of a Major Role for Herpes Simplex Virus Type 1 in Alzheimer's Disease* [42], Dr. Ruth Itzhaki again mentions: "*The main initial discovery on which this concept* [*the viral concept of Alzheimer's disease*] *was based was that HSV1 DNA was detectable in brain of both AD patients and elderly normal people* [*i.e., the latter were infected but were asymptomatic; Jamieson et al. 1991*]*, the two groups differing in that most of the AD patients were APOE-ε4 carriers."* (Itzhaki et al. 1997). Yet in this same publication, Itzhaki seems to challenge her own hypothesis that latent HSV1 in brain of carriers of the type 4 allele of the apolipoprotein E gene (APOE-+4) is reactivated intermittently by events such as immunosuppression, peripheral infection, and inflammation…..by adding this: "*The data cannot be explained by a greater susceptibility of AD sufferers, or of APOE-ε4 carriers, to HSV1 infection, as the virus was present in brain at almost the same frequency in AD patients as in the controls, and was far more frequent among non-APOE-ε4 carriers than among APOE-ε4 carriers in the controls (although admittedly, the numbers in each category were very small).*" Such seeming contradiction is puzzling, unless her postulated "reactivation" is based upon an underlying "peripheral infection" with its accompanying immunosuppression and inflammation other than the HSV-1 virus to begin with, which is entirely possible.

In the same paper, Professor Itzhaki speaks of Tzeng's recent Taiwan herpes study saying "*The striking results included evidence that the risk of senile dementia is much greater in those who are infected with HSV, and that anti-herpes antiviral treatment causes a dramatic decrease in numbers of those subjects severely affected by HSV-1 who later develop dementia*". First of all, Tzeng, in actuality, couched his terms very carefully, stating that HSV infection "may have" a 2.56-fold increased risk of developing dementia. Second, with regard to the usage of anti-herpetic medications for a decreased risk of dementia [38], Tzeng seemed oblivious to Helmer's [37] earlier study, which found that anti-herpetic medicines such as acyclovir were "not significant" for lessening dementia. Furthermore, there are unresolved issues regarding the anti-herpetic agents themselves, which Kruszewska found to have antibacterial properties [39] and Pochet [43] and others [44] showed had anti-mycobacterial properties. Ignored are studies like that of Kooy [45], who found not a virus, but members of the family *Mycobacteriaceae* in febrile herpes. Yet no attempt to the present has been made to detect this group, which, according to Hirsch, are probably the most immunosuppressive microorganisms currently on the planet [46, 47]. Nevertheless, the little-cited but intimate relationship between the herpes virus and such immunosuppressive *Mycobacteriaceae* was shown by Hippmann [48], who through a single intracutaneous injection of BCG (dilute cow tuberculosis or *Mycobacterium bovis*), which has the capacity to kill *Mycobacterium tuberculosis* efficiently [49], also reduced the subsequent occurrence of herpes lesions by this same injection, keeping 19% of patients completely herpes free for 3 years and 9% herpes free for more than 6 years.

Regarding Dr. Ruth Itzhaki's conclusions, Dr. David Reynolds, Chief Scientific Officer at Alzheimer's Research UK, said: "*This review presents mainly correlative studies that do not give clear evidence of cause and effect. The evidence presented in this review is not sufficient to suggest that Alzheimer's disease is contagious and be passed from person to person like a virus and neither does it mean that having cold sores increases your risk of getting dementia*" [50].

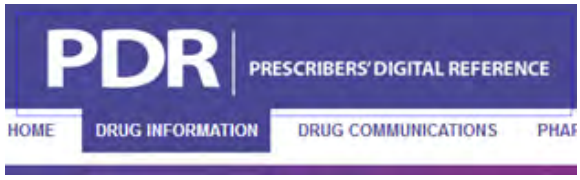
## Conclusion

One is well served to remember that some scientists were certain that a virus was behind Lyme disease, mycoplasma pneumonia, and Legionnaires' disease before their respective bacteria were found. Also, approximately 50 years ago, German national and virologist Harald zur Hausen hypothesized that the virus called papilloma, said to be responsible for ordinary warts, also caused cervical cancer. Most thought zur Hausen's thoughts rather bizarre. Another "virus", called Herpes Simplex, had already been implicated as causing cervical cancer. And so, in 1974 at a meeting in Key Biscayne in Florida, specifically scheduled to validate Herpes Simplex type 2 as the cause of cervical cancer, zur Hausen was the lone and most unwelcomed voice in the room reporting negative results in trying to find herpes simplex type 2 DNA in cervical cancer cells. Zur Hausen was finally accredited with his discovery that human papillomaviruses cause cervical cancer by winning the Nobel Prize in Medicine in 2008.

Is it then possible that both a putative microbe and an accompanying virus can be responsible for a disease? Of course it is and we have no further to look then the present AIDS epidemic, in which the Mycobacteriaceae are the leading cause of death [51]. In addition, all virulent bacterial or mycobacterial pathogens have phages (bacterial viruses) incorporated into their DNA which Mankiewicz showed in the case of mycobacteriophage could even go to the extent of causing premalignant tissue change [52]. But as long as viral research is conducted with tunnel vision it will be difficult to test this hypothesis for AD.

In the meantime, in her *Corroboration of a Major Role for Herpes Simplex Virus Type 1 in Alzheimer's Disease*, Itzhaki, seems to be suggesting the almost reckless use of "anti-herpetic antivirals" to treat Alzheimer's disease [AD]: "*Three publications have now appeared describing data on the development of senile dementia (SD), and the treatment of those with marked overt signs of disease caused by varicella zoster virus (VZV), or by HSV. The striking results show that the risk of SD is much greater in those who are HSV-seropositive than in seronegative subjects, and that antiviral treatment causes a dramatic decrease in number of subjects who later develop SD. It should be stressed that these results apply only to those with severe cases of HSV1 or VZV infection, but when considered with the over 150 publications that strongly support an HSV1 role in AD, they greatly justify usage of antiherpes antivirals to treat AD*" [42]. Actually, the 150 publications cited pale in comparison to the thousands of publications that laced Medline proclaiming Gallo's HTLV-1 virus as the cause of AIDS –before these were all proven wrong.

The potentially dire consequences of such off-label suggested use of anti-herpetics are listed below and in the Prescribers' Digital Reference of the PDR (Physicians' Desk Reference) in the form of a multitude of adverse reactions, many of them severe, with "incidence not known": [https://www.pdr.net/drugsummary/acyclovir?druglabelid=670]




**Acyclovir sodium - Drug Summary**

**Adverse Reactions**

| Severe | Moderate |
|---|---|
| Coma/Early/1.0-1.0<br>Seizures / Delayed/1.0-1.0<br>Renal Tubular Obstruction/Delayed/Incidence Not Known<br>Azotemia / Delayed/Incidence Not Known<br>Renal Failure (Unspecified)/Delayed/Incidence Not Known<br>Tissue Necrosis/Early/Incidence Not Known<br>Stevens - Johnson syndrome/Delayed/Incidence Not Known<br>Erythema Multiforme/Delayed / Incidence Not Known<br>Toxic Epidermal Necrolysis/Delayed/Incidence Not Known<br>Hemolytic-Uremic Syndrome/Delayed/Incidence Not Known<br>Thrombotic Thrombocytopenic Purpura (TTP)/Delayed/Incidence Not Known<br>Anaphylactoid Reactions/ Rapid/ Incidence Not Known<br>Angioedema/Rapid/Incidence Not Known<br>Visual Impairment/Early/Incidence Not Known<br>Vasculitis/Delayed/Incidence Not Known<br>Disseminated Intravascular Coagulation (DIC)/Delayed/Incidence Not Known | Thrombocytopenia/Delayed/0-1.0<br>Neutropenia/Delayed/0-1.0<br>Thrombocytosis/Delayed/0-1.0<br>Stomatitis/Delayed/1.0-1.0<br>Crystalluria/Delayed/Incidence Not Known<br>Delirium/Early/Incidence Not Known<br>Ataxia/Delayed/Incidence Not Known<br>Psychosis/Early/Incidence Not Known<br>Dysarthria/Delayed/Incidence Not Known<br>Hepatitis/Delayed/Incidence Not Known<br>Hyperbilirubinemia/Delayed/Incidence Not Known<br>Jaundice/Delayed/Incidence Not Known<br>Edema/Delayed/Incidence Not Known<br>Contact Dermatitis/Delayed/Incidence Not Known<br>Hypotension/Rapid/Incidence Not Known<br>Peripheral Edema/Delayed/Incidence Not Known<br>Hemolysis/Early/Incidence Not Known<br>Leukopenia/Delayed/Incidence Not Known<br>Hematuria/Delayed/Incidence Not Known<br>Lymphadenopathy/Delayed/Incidence Not Known |

| Moderate | Mild |
|---|---|
| Phlebitis/Rapid/9.0-9.0<br>Elevated Hepatic Enzymes/Delayed/1.0-2.0<br>Hallucinations/Early/1.0-1.0<br>Confusion/Early/1.0-1.0<br>Encephalopathy/Delayed/1.0-1.0<br>Erythema/Early/1.0-1.0<br>Anemia/Delayed/0-1.0<br>Lethargy / Early / 1.0-1.0<br>Tremor / Early / 1.0-1.0<br>Dizziness / Early / 1.0-1.0<br>Agitation / Early / 1.0-1.0<br>Leukocytosis / Delayed / 0-1.0<br>Drowsiness / Early / Incidence Not Known<br>Paresthesias / Delayed / Incidence Not Known<br>Fatigue / Early / Incidence Not Known<br>Abdominal Pain / Early / Incidence Not Known | Skin Irritation/Early/1.0-30.0<br>Malaise/Early/11.5-11.5<br>Injection Site Reaction/Rapid/9.0-9.0<br>Nausea/Early/2.4-7.0<br>Vomiting / Early/2.7-7.0<br>Pruritus/Rapid/1.0-4.0<br>Diarrhea/Early/2.4-3.2<br>Headache/Early/2.2-3.0<br>Rash/Early/1.0-2.0<br>Anorexia / Delayed / Incidence Not Known<br>Photosensitivity / Delayed / Incidence Not Known<br>Urticaria / Rapid / Incidence Not Known<br>Xerosis / Delayed / Incidence Not Known<br>Alopecia / Delayed / Incidence Not Known<br>Fever / Early / Incidence Not Known<br>Myalgia / Early / Incidence Not Known |

And the above list does not even include drug interactions, of which there are many.

Itzhaki and her group believe that the mechanism through which herpes takes hold in the brains of the elderly is through reactivation as a result of the natural process of immunosuppression which comes with aging, but cannot rule out that such immune suppression is not as a result of previous infection by other microbes [53]. And therein lies the rub in any discussion of a viral cause for Alzheimer's: is there an underlying bacterial or mycobacterial pathogen providing the immunosuppression through which the herpes virus flourishes and is therefore picked-up coincidentally? Certainly all of the recent viral attributes toward causing amyloid and tau have a much firmer historical and experimental basis in non-viral pathogens. Since Contini, who in 2010 reviewed the history of viruses attributed to causing Alzheimer's, which included the measles virus, the adenovirus, lentiviruses, hepatitis C, cytomegalovirus and several others –we have the recent announcement that two other types of herpes: Human Herpes Virus-6A (HHV-6A, cause of roseola, a common childhood illness), and Human Herpes Virus-7 (like HHV-6, principally acquired in infancy and childhood and also able to cause roseola) are twice as high in the brains of people with Alzheimer's as those without [54]. Yet Emery in 2017 [55] found

*Actinobacteria*, a class that like the *Mycobacteriaceae* belongs to the *Actinomycetales*, to be 10 times as high in the brains of people with Alzheimer's as those without –and again many find themselves asking as to whether the numerous viruses attributed to Alzheimer's to this point could not merely be passenger viruses, activated by some underlying immunosuppressive disease process or age itself. So if there is abundant doubt that viruses are in anyway causative for Alzheimer's, that doubt is not without foundation.

**Authors' Declaration**

The authors declare absolutely no competing financial and/or non-financial interests in relation to this work.

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