The case for a trial of antiviral agents to treat Alzheimer's disease patients, and effects of prior treatment on subsequent risk of dementia.

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Abstract
We discovered that many elderly people, herpes simplex virus type 1 (HSV1) DNA is present latently in brain, and that it confers a strong risk of Alzheimer's disease (AD) when in brain of APOE-e4 carriers. Subsequently, we suggested that HSV1 reaches the brain probably as the immune system declines and that as in the PNS it is reactivated periodically from latency by events such as stress, peripheral infection, etc. The resulting damage - direct viral action and virus-induced inflammation - then accumulates, leading eventually to AD. We then investigated antiviral treatment of HSV1-infected Vero cells. We used acyclovir (ACV), which interferes with viral DNA replication, and found that the accumulation of beta amyloid and especially of AD-like-tau in the cells was greatly reduced (Wozniak et al., 2011). Several other antivirals with different modes of action showed the same protective effect. Fucoidan, a sulphated polysaccharide derived from seaweed, used in combination with ACV showed a synergistic effect (Wozniak et al 2015). Very intriguingly, several recent studies suggest that treatment of subjects with severe herpetic disease are protected against subsequent risk of dementia. There were indications that varicella zoster virus (VZV) is implicated as well as HSV1, although VZV's role might be indirect. All the data support a causal role for HSV1 (and possibly of VZV too) in AD and support also the antiviral data from the author's laboratory. The case is therefore strong for antiviral treatment of AD patients with valacyclovir (the biodrug of ACV), perhaps together with fucoidan: this combination might well slow or even stop the deterioration of the patients.

Keywords: HSV1, antivirals, valacyclovir, acyclovir, fucoidan, AD treatment.

JEL Classification: H42, I11

Rationale for treatment of AD patients with anti-herpetic antivirals

The possibility of treatment of AD patients with antiviral arose from the discovery by the author's lab that in many elderly people, herpes simplex virus type (HSV1) DNA is present latently in brain (Jamieson et l 1991), and that it confers a strong risk of AD when in brain of APOE-e4 carriers (Itzhaki et al. 1997). In striking parallelism in the peripheral nervous system, we found that APOE-e4 is a risk for cold sores, herpes labialis, which is caused usually by HSV1(Itzhaki et al., 1997). By examining cerebrospinal fluid, we were able to show evidence of reactivation of the latent virus w 2005, and subsequently, we suggested that HSV1 reaches the brain probably as the immune system declines and that as in the PNS, it is reactivated periodically from latency by events such as stress, peripheral infection, etc. The resulting damage – through direct viral action and virus-induced inflammation - then accumulates, leading eventually to AD (Wozniak et al, 2010).

We then found links between viral action on cells in culture and the pathological features of AD brains: immunocyto- or immunohistochemistry, HSV1-infected cells in culture and also brains of infected mice, displayed accumulation of beta amyloid (Abeta), and the infected cells showed also accumulation of AD-like tau. Examining sections of brain by *in situ* PCR revealed that the HSV1 DNA was located very precisely within amyloid plaques. Some 80-90% of plaques in control and AD brains contained the viral DNA. In the case of AD brains, 72% of the DNA co-localised but in elderly normal brains only 24 % co-localised (we were able to discount artefactual co-localisation.) This discovery of co-localisation in AD suggested that plaque formation was induced by HSV1 and that Abeta entrapped the viral DNA in AD amyloid plaques (Wozniak et al., 2009.

All these results suggested that HSV1 in brain of APOE-e4 carriers is a cause of AD and that antiviral treatment to prevent its action might slow or even stop disease progression.

Treatment of infected Vero cells with Acyclovir (ACV), pencyclovir (PCV), and Foscarnet.

We then investigated antiviral treatment of HSV1-infected cells in culture, using the level of Abeta and of P-tau in untreated and antiviral-treated cells as measures of efficacy of the antiviral in combatting HSV1 action. We first used acyclovir (ACV)to treat HSV1-infected Vero cells. ACV interferes with viral DNA replication. It is a nucleoside analogue which requires an HSV1 enzyme, thymidine kinase, for phosphorylation to its monophosphate form; subsequently, cell kinases phosphorylate it to the diphosphate form and the triphosphate form. It then competes with normal substrates taken up during viral DNA synthesis and prevents further strand elongation. Thus ACV "finds" HSV1-infected cells & stops HSV1 replication. In practice, valacyclovir, the biodrug of ACV, is used orally as its absorption is very much greater than that of ACV.

We initially considered that as ACV is an inhibitor of HSV1 DNA replication, it would be successful only if Abeta and P-tau accumulation were replication-dependent. We therefore investigated the stage of the virus replication cycle at which Abeta and P-tau were produced in infected cell cultures, using ACV and various recombinant strains of HSV1 (Wozniak et al., 2011). We found that P-

tau production depended on HSV1 DNA replication, whereas that of Abeta depended on an earlier event in the virus replication cycle, after virus entry. Nonetheless, ACV reduced greatly not only the HSV1-induced accumulation of P-tau but also reduced but to a lesser extent that of Abeta; we attributed the latter to the decrease in HSV1 DNA replication causing decreased viral production and hence decreased cell-to-cell spread of virus.

Two other antivirals with similar modes of action - penciclovir and foscarnet - showed the same protective effect, reducing Abeta and P-tau accumulation, as well as HSV1, with foscarnet being less effective in each case. Again, P-tau accumulation was found to depend on HSV1 DNA replication, whereas Abeta accumulation was not.

Treatment of infected Vero cells with BAY 57–1293

We then investigated BAY 57–1293, a non-nucleosidic inhibitor of the HSV helicase-primase complex, i.e., it acts at different stage of viral DNA replication from that of ACV. This complex unwinds the double-stranded viral DNA and synthesises oligoribonucleotide primers for DNA synthesis by the viral DNA polymerase. Thus, it functions at the viral replication fork. BAY 57–1293 was found to be active against HSV1 mutants, and to be nearly two orders of magnitude more potent than ACV in vitro, as judged by cytopathogenicity and plaque reduction assays. We found that BAY 57–1293 is more efficient than ACV not only in inhibiting HSV1 replication, confirming previous studies, but also in decreasing Ab and P-tau formation. Also, the cell clusters that were formed during infection were reduced in size much more efficiently by BAY 57–1293 than by ACV Wozniak et al.(2013) These data suggest that BAY 57–1293 would be a more effective agent than ACV for treating AD

Treatment of infected Vero cells with intravenous immuno-globulin (IVIG)

Our next investigation was on intravenous immunoglobulin (IVIG), which is a therapeutic product derived from the pooled plasma of thousands of people, and is used for treating immune-deficient patients who have reduced antibody levels. IVIG has been tried also as a treatment for AD, the rationale being that it contains antibodies against the toxic protein Abeta (IVIG is thus thought to augment the presumed relatively low level of the patients' Aβ antibodies, thereby enhancing Abeta clearance). However, although treatment led to some encouraging preliminary effects on cognitive function, the usage of monoclonal anti-Abeta antibodies for treatment has not yet done so. Possibly, in the positive preliminary studies, IVIG might have affected some factor other than Abeta, perhaps through its antiviral properties. IVIG contains large amounts of neutralising antibodies to many microbes and so in AD patients it might have inhibited the action of HSV1, against which IVIG is known to have antiviral action.

Our main finding was that in HSV1-infected Vero cells, Privigen (the IVIG product that we used) causes statistically significant reductions, particularly at higher concentrations, in levels of Aβ and P-tau, as well as in HSV1 proteins. This probably results from Privigen preventing viral entry into cells; thus, few viruses would enter the cells and few cells would be stained. Also, Privigen and ACV added together act synergistically, causing statistically significant reductions in these levels, presumably resulting from the

combination of prevention of viral entry and inhibition of DNA replication of any virus that has evaded the prevention. These data suggest that Privigen would be a suitable antiviral agent for treating AD, and that its action would be even more effective if used in combination with ACV.

Treatment of infected Vero cells with Fucoidans

The next antiviral we investigated were fucoidans (known also as fucans, sulphated polysaccharides derived from seaweed (Wozniak et al 2015). Their antiviral action is attributed to their prevention of virus binding to receptors in the cell surface through interaction with positively charged domains in the viral envelope glycoproteins; this causes also a virucidal effect. We found that sulfated fucans with different structures extracted from several species of brown algae prevented the HSV1-induced accumulation of Abeta and P-tau. The combination of the most active fucan (a galactofucan sulfate from U.pinnatifida) with ACV was particularly effective, showing synergism.

Antiviral treatment of infected neural-type cells, and usage of 3D cultures.

An important investigation into antivirals relating more directly to brain than did previous studies using Vero cells, was that of Cairns et al (2020) using neural stem cells in 2D and 3D brain model systems. These cells, on treatment with HSV1, developed several major features of AD including accumulation of beta amyloid and AD-like tau, gliosis, neuroinflammation, and decreased functionality, and ACV treatment was protective against the HSV1-induced changes. Their AD model strongly supports a causal role for HSV1 in AD and supports also the antiviral data from the present author's laboratory. The case is therefore strong for antiviral treatment of AD patients with VCV, perhaps together with fucoidan: this combination might well slow or even stop the deterioration of the patients.

Studies on treatment with antivirals prior to any onset of dementia and role of VZV in dementia

It is now accepted that infections increase the risk of dementia/AD and there is some evidence that certain types of vaccination reduce the risk. One proposed explanation was that infections cause neuroinflammation and hence, reactivation of HSV1 in brain, and that vaccinations prevent this occurrence (Itzhaki and Dobson, 2002). This suggests that future prevention of infections by antiviral treatment might reduce the risk of AD.

Three important epidemiological studies from Taiwan, where health insurance data for 99.9% of the population is available, investigated the effect of antivirals used for treating herpes infections before any signs of dementia appeared. Chen et al., examined the frequency of later SD development in patients aged 50–90 years diagnosed with herpes zoster (HZ - shingles) infection in the period 1997–2013, with a mean follow-up period of 6.2 years. They compared dementia outcomes in 39,205 HZ patients and 39,205 controls. They found that the incidence of dementia increased only marginally in the HZ patients (risk ratio 1.11,95% CI 1.04–1.17; p = 0.0014). However, when Chen et al. investigated HZ patients treated with antiviral therapy (AVT), including acyclovir, tromantadine, famciclovir, valacyclovir, all of which target VZV as well as HSV1, comparing treated with untreated HZ

patients, there was a major effect on the outcome. The risk of dementia in HZ patients receiving AVT was reduced by a factor of 0.47 (adjusted 0.55; 95% CI 0.34–0.65 and 0.40–0.77). The likelihood of HZ patients receiving AVT to develop dementia was therefore halved during the follow-up period, a highly significant result ($p < 0.0001$). VZV has not so far been suggested as a prospective cause of dementia, and the sole study that searched for VZV DNA in brain of aged normal people and of AD patients by PCR failed to detect it (sensitivity: <10 VZV sequences per sample). However, the effect of VZV might be indirect: inflammation (a known reactivator of latent HSV1) caused by VZV infection could lead to reactivation of latent HSV1 in brain (see below).

Tsai et al. (2017) investigated 846 patients (mean age 61.6 years) diagnosed with herpes zoster ophthalmicus (HZO), which is caused by VZV, in 2005, to find their subsequent risk of dementia compared with that of an age-matched control group of 2,538. They found that 4.16% HZO patients developed SD within the 5-year follow-up period, versus 1.65% in the controls ($p < 0.001$) – representing a relative risk ratio being almost 3. No information on antiherpetic medication and effect on dementia risk was provided.

Tzeng et al. (2018) using the same database, identified 8,362 subjects aged ≥50 years during the period January to December 2000 who were newly diagnosed with HSV (HSV1 or HSV2) infection and who had made **at** least three outpatient visits within the index year; the significance of this was not specified but presumably it reflected a pronounced severity and recurrence of infection, such as genital ulceration and/or severe herpes labialis. These subjects were compared with a control group of 25,086 people with no HSV infection during the index year. The occurrence of dementia during the next 10 years (2001–2010) was followed. The risk of dementia in the HSV-infected group was increased by a factor of 2.564 (after statistical adjustment, 95% CI 2.351–2.795; $p < 0.001$), and was much greater than the risk associated with general VZV infection (1.11, Chen et al.). Most of the infections were caused by HSV1, although there was a small risk associated with HSV2. Both AD and vascular dementia showed similar risk profiles. Anti-herpetic treatment caused a dramatic reduction in the later incidence of dementia, the overall risk in the 10-year follow-up period was reduced by at least 80% (adjusted relative risk factor was 0.092, 95% CI 0.079–0.108, $p < 0.001$) in those receiving any of antiviral medications, compared to individuals who received no AVT; protection was greater in those treated for longer time periods (>30 days versus <30 days).

A study by Bae et al (2020) using National Health Insurance Service data in Korea analysed 229,594 individuals aged ≥50 years. Patients with HZ had a higher risk of dementia - adjusted hazard ratio [HR], 1.12 [95% CI 1.05–1.19]). Of the 34,505 patients with HZ, 28,873 (84%) had received antiviral treatment (acyclovir, famciclovir, or valaciclovir). The treated group showed a significantly lower risk of dementia (HR 0.76; 95% CI 0.65–0.90). No details of duration or dosage were available in the databank. However, in this large population-based cohort study, HZ was associated with a higher risk of dementia, and treatment of HZ patients with antiviral agents was associated with lower risks of dementia, results broadly resembling those of Chen et al and Tsai et al

Schnier et al. (2021) investigated the linked electronic health records of 2.5 million individuals aged ≥65 years in national observational cohort studies on populations in four different

countries. The basis of the diagnosis of HSV1 is not mentioned but presumably, as antiviral treatment was given, the symptoms were obvious, although the fact that it was stated that most subjects were given only a single prescription for only 1-2 weeks suggests that the illness was mild; presumably the VZV cases were mild also. The authors found that in the Danish and Welsh cohorts, people who were prescribed at least one dose of herpes antiviral medication, mainly ACV and VCV) had up to an 11 percent decrease in dementia risk; however, they considered this might well result from confounding factors, while the two other cohorts, in Germany and Scotland, showing no altered risk. The dementia outcome was unaffected by type of herpesvirus.

A very recent study by Lopatko Lindman et al.(2021)in Sweden investigated 265,172 subjects aged ≥ 50 years, diagnosed with VZV or HSV1 infection, between the years 2005 and 2017, some of whom were treated with antivirals, mainly VCV and ACV. Data of viral diagnoses and antiviral treatment were collected from two nationwide databases: the National Patient Register (NPR) and the Swedish Prescribed Drug Register. The authors stated that HSV and VZV diagnoses in Sweden are usually based on physical exams with the presence of typical rashes and distribution; presumably, this means that in the case of HSV1 the subjects had severe herpes labialis and in the case of VZV, the subjects had HZ. Controls without herpes diagnoses and without antiviral treatment were matched randomly in a 1:1 ratio by sex and year of birth. There were more cases of VZV infection than of HSV infection (4323 and 5722 with no antiviral treatment, respectively, and 24,045 and 6510 with antiviral treatment, respectively, and in some cases, the subjects revealed infection with both viruses). The authors compared cases without antiviral treatment to those prescribed antiviral drugs at least once. They were unable to study any dosage- or duration-related effects, as there was no adequate information in the databases; However, the standard dosage for treatment of herpes zoster reactivations, according to Swedish clinical guidelines, is VCV 1000 mg three times a day for 7 days or ACV 800 mg five times a day for 7 days. They found that VZV and/or HSV-infected subjects not treated with antivirals had an increased risk of dementia (adjusted HR 1.50, 95% CI 1.29 to 1.74), and that antiviral treatment reduced the risk of dementia (adjusted hazard ratio [HR] 0.89, 95% confidence interval [CI] 0.86 to 0.92),
The involvement of VZV in the study by Lopatko Lindman et al. supports the four previous findings (Tsai et al., 2017; Chen et al., 2018; Bae et al., 2020; Schnier et al., 2021) in showing that VZV, like HSV1, confers a risk of dementia, although (except in the case of HZO)it is very small. However, recent epidemiological and serological studies by RFI and colleagues indicate that vaccination against shingles substantially reduces the risk of dementia (Lophatananon et al., 2021; Mekli et al., submitted). Also, studies on the brain model cultures of human induced neural stem cells suggest that VZV action is indirect and that it does indeed cause reactivation of HSV1 (Cairns, Itzhaki and Kaplan, submitted).
As to whether or not the action of VZV is direct, i.e., resulting from its being present in brain and its subsequent reactivation there, or whether instead it is indirect, acting via inflammatory processes which cause reactivation of HSV1 resident in brain is uncertain. (Such indirect, inflammation-induced reactivation of HSV1 in the CNS could presumably be caused also by infective agents other than VZV in the PNS (Wozniak and Itzhaki, 2010). In fact the present author's lab sought VZV DNA in brain (Lin et al, 1997) but did not detect it, whereas Hemling et al. did find it, though they did not detect HSV1 DNA (surprisingly in the case of VZV, as their detection

of the DNA of both viruses was far less sensitive than that of Wozniak and Itzhaki). Involvement of VZV in dementia has been suggested by other approaches, such as the study by Grahn et al (2013) which showed that after acute VZV infection, patients who had suffered predominantly CNS manifestations showed significant cognitive decline 3 years later.

It would be of great interest to discover whether or not VZV does reside in the brain and to discover whether HSV1 is the sole neurotropic virus (or bacterium) resident there. Other more minor points of interest which need to be elucidated, though they are often not specified in such databases, is whether HSV means HSV1 or, far less likely, HSV2 - genital herpes; also, APOE genotypes, and details of the type, duration, etc., of the antiviral used would be valuable.

The results of Schnier et al. showing little or no effect of antiviral treatment on subsequent dementia differ from those of the two Taiwan studies, and of Bae et al and Lopatkin Lindman, all of which showed that pre-treatment of herpes infections with antivirals reduced the risk of subsequent dementia. This very probably relates to the much longer duration of antiviral treatment, in the studies in which duration data were available, than in that of Schnier et al. It is likely also that their "controls" included subjects asymptomatically infected with HSV1, which would reduce any disparity between control and infected groups (Itzhaki, 2022).

How can the protective effect of antivirals on risk of dementia be explained?

The actual sequence of events affording this protection is unknown. As the present author and Richard Lathe pointed out (Itzhaki and Lathe, 2018), the protective effect is extremely puzzling, because after each treatment the antiviral would have remained in the body for only a few days, and much would have been excreted. We suggested one possible explanation, based on research by my group some 24 years ago (Itzhaki et al; 1997) suggesting that the virus, which resides in the PNS of most adults, might travel from the PNS to CNS in older age as the immune system declines. Assuming that this suggestion is correct, we speculated that antiviral treatment might prevent the transit of HSV1 into the brain, or possibly delay its transit. If so, extending the Taiwan survey for 5–10 years could determine whether dementia cases later increase in the treated cohort (Itzhaki and Lathe, 2018). Investigations to seek HSV1 DNA in the brain *post mortem* of any such subsequent cases of dementia, and of those who remained free of the disease, might help to elucidate the situation.

Alternatively, in older people, if the virus has already reached the brain, the antiviral might reduce the frequency of reactivation – as intimated by Lopatko Lindman et al. However, an argument against both suggestions would be that even the longer durations of treatment or the more frequently given doses, as in the current study, would presumably have been rendered ineffectual eventually by subsequent passage of the virus to the CNS, or resumption of its usual reactivations in the CNS. Thus, the mystery of the effectiveness of prior antiherpetic treatment in reducing the risk of subsequent dementia remains to be solved.

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