Herpes Viruses and Senile Dementia: First Population Evidence for a Causal Link

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Herpes Viruses and Senile Dementia: First Population Evidence for a Causal Link

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Three articles have very recently appeared that are of especial relevance to the causes of dementia and its potential treatment. The first two (Tsai *et al.,* published in *PLoS One* in November 2017, and (Chen *et al.*, published in the January/February 2018 issue of *Journal of Clinical Psychiatry*) demonstrate an increased risk of subsequent senile dementia (SD) development in patients with acute varicella zoster (herpes zoster) infection. These articles present data highly relevant to the third, and most important, paper – by Tzeng *et al.*, published online in the journal *Neurotherapeutics* at the end of February 2018. These authors report that infection with a different herpes virus, herpes simplex virus type 1 (HSV1), leads to a similarly increased risk of later developing SD. Further, when the authors looked at patients treated aggressively with antiherpetic medications at the time, the relative SD risk was reduced by a factor of 10. It should be stressed that no investigations were made on subjects already suffering from SD, and that those treated were the few rare cases severely affected by HSV. Nonetheless, antiherpetic medication prevented later SD development in 90% of their study group. These articles provide the first population evidence for a causal link between herpes virus infection and senile dementia.

INTRODUCTION

Alzheimer disease (AD) is a devastating neurological disorder that principally affects the elderly, but no effective treatments are yet available. Therapeutic approaches have focused on removing the AD signature peptide Aβ, but these have, without exception, been unsuccessful. Findings that infectious agents such as herpes viruses are present in brain and can induce Aβ and AD-like tau, the main components of the abnormal features of AD brains, have led to the proposal that herpes virus infection, in particular, might underlie some cases of senile dementia (SD) ([1] for overview). Recent work from Taiwan casts new light on this issue.

Most of the population harbors latent infections with several types of herpes viruses that are acquired during their lifetimes. Infection rates in neonates are very low but, in the case of herpes simplex virus type 1 (HSV1), by age 70 years some 80–90% or more of the population is seropositive. The virus is present also in brain [2] in many elderly people and AD patients, and it was proposed that sporadic reactivation of latent HSV1 in the brain, particularly in *APOE-ε4* carriers, might confer an increased risk of later developing AD [2]. (Also, *APOE-ε4* was found to be a risk for cold sores, which are caused usually by HSV1). However, validation of a viral link demands epidemiologic evaluation at the population level, a logistically daunting task because sufficiently comprehensive data are not available in most countries.

By contrast, in Taiwan researchers are beginning to interrogate the Taiwan National Health Insurance Research Database. This database was launched in 1995, and as of 2014 99.9% of the population has been enrolled (https://nhird.nhri.org.tw/en/). Thought-provoking findings are now beginning to emerge, and we highlight three recent papers that begin to address potential links between herpes virus infection and SD.

VARICELLA ZOSTER VIRUS (VZV)

The first two studies focus on VZV, a herpes virus that causes chickenpox and which, like HSV1, remains in the body for life. In some people VZV reactivates in older age causing shingles, referred to as herpes zoster (HZ), and when the eye is involved, as herpes zoster ophthalmicus (HZO).

In the first paper, published in *PLoS One* in November 2017, Tsai *et al.* [3] looked at the risk of dementia in patients (mean age 61.6 years) diagnosed with HZO as of 2005, and examined whether they later developed SD. They studied a target HZO group of 846 patients, contrasted with an age-

matched control group of 2538. Of patients with HZO, 4.16% developed SD within the 5 year follow-up period, versus 1.65% in the controls ($P<0.001$). This represents a relative risk ratio of developing SD within 5 years of HZO diagnosis of 2.82–2.97 (depending on statistical adjustment), a finding comparable to the relative risk (ca. threefold) associated with harboring a single *APOE* □*4* risk allele ([4]; reviewed in [5]).

The second paper, by Chen *et al.* [6], published in the January/February 2018 issue of the *Journal of Clinical Psychiatry*, examined the frequency of later SD development in patients aged 50–90 years diagnosed with VZV infection in the period 1997–2013, with a mean follow-up period of 6.2 years. They compared SD outcomes in 39 205 VZV patients versus 39 205 controls.

In this study the incidence of SD was only marginally increased in the VZV patients (risk ratio 1.11, 95% CI 1.04–1.17; $P=0.0014$), in contrast to the major increase after HZO. Possibly in HZO there is a greater likelihood of the virus reaching the brain (as opposed to the peripheral infections in most VZV patients). However, when Chen *et al.* compared VZV patients treated with antiviral therapy (AVT, including all forms of acyclovir, tromantadine, famciclovir, valacyclovir) versus untreated VZV patients, there was a major effect on the outcome. The risk of SD in VZV 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) [6]. In other words, VZV patients receiving AVT were half as likely to develop SD during the follow-up period, a highly significant result ($P<0.0001$).

Although the potential involvement of herpes viruses in SD has been widely debated, VZV itself has not so far been suggested as a prospective cause of SD. 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) [7]. However, the finding that AVT (the agents used by Chen *et al.* block the replication of both VZV and HSV, but have no effect on the latent viruses) reduces the risk of later SD is consistent with other interpretations. Because the immune system declines with age, some older people (notably carriers of risk alleles of immunomodulatory APOE) may be more susceptible to infections. Inflammation (a known reactivator of latent HSV1) occurring as a result of infection (e.g., with VZV) could then lead to reactivation of other latent viruses in brain. The majority of the adult population already harbors latent infections with viruses such as HSV1, but there is direct evidence that infection with another herpes virus, cytomegalovirus, can reactivate HSV1 [8]. This was attributed to the increased reactivation rate of CMV on aging (which, the auth found, applied also to another herpesvirus, Epstein-Barr virus [Stowe et al., 2007].) Hence,

suppression of some VZV infections by AVT medication could plausibly reduce the likelihood of reactivation of other related viruses and the resulting damage.

HERPES SIMPLEX VIRUS (HSV)

The third paper, by Tzeng *et al.* [9], now published online in the journal *Neurotherapeutics*, is equally intriguing. Using the same database, the authors identified 8362 subjects aged ≥50 years during the period January to December 2000 who were newly diagnosed with HSV (HSV1 or 2) infections. Infection was defined as at least three outpatient visits within the index year, which presumably means that all the patients had recurrent and severe overt signs of infection such as genital ulceration and/or severe herpes labialis. In each case HSV infection was confirmed by ELISA, antibody test, or PCR. This study group was compared to a control group of 25 086 age- and gender-matched individuals with no HSV infection history during the index year. The authors then monitored the development of SD in these individuals over a follow-up period of 10 years (2001–2010).

The risk of developing SD in the HSV group was increased by a factor of 2.542 (2.564 after statistical adjustment, 95% CI 2.351–2.795; $P<0.001$), comparable to the risk associated with ophthalmic VZV infection (2.82–2.97, Tsai *et al.* [3]), but well above the risk associated with general VZV infection (1.11, Chen *et al.* [6]). The effect was largely restricted to HSV1 infections, although a small risk associated with HSV2 was also noted. When SD was subtyped into AD and vascular dementia, similar risk profiles were found in both cases.

Remarkably, when the authors compared those among the HSV cohort who were treated with AVT (the same agents as those examined by Chen *et al.*) at the time, versus those who did not receive AVT, there was a dramatic reduction in the later incidence of SD. The overall risk of SD development in the 10 year follow-up period was reduced by at least 80% (adjusted relative risk factor = 0.092, 95% CI 0.079–0.108, $P<0.001$) in those receiving any one of several AVT medications, compared to individuals who received no AVT; protection was greater in those treated for longer times (>30 days versus <30 days).

Not only is the magnitude of the AVT effect remarkable, but also the fact that – despite the relatively brief duration of treatment – AVT appeared to prevent the long-term damage in brain that results in SD. The mechanism by which AVT might prevent later-life SD development remains unknown. To speculate, it could reduce the likelihood that HSV1 in the periphery reaches the brain,

based on the assumption that passage generally occurs in middle age when the immune system starts to decline. The Taiwan study group (≥50 years of age) subjects were selected as having newly diagnosed HSV infection, although whether they had newly acquired infection or reactivation of existing (latent) infection is uncertain. In either case, however, AVT would greatly reduce viral replication in the periphery, thereby reducing the likelihood that peripheral virus travels to the brain. Because AVT treatment might only delay (rather than prevent) transmission to the brain, extending the Taiwan survey for 5–10 years could determine whether SD cases later increase in the treated cohort. Investigation 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.

CAVEATS AND CONCLUSIONS

To our knowledge, these three papers provide the first population-level evidence for a link between herpes infection and later SD development, and of the possible preventive efficacy of AVT – with potential implications for the clinical management of acute infections with HSV and VZV. Although the antiviral agents employed are very specific against the Herpesviridae, the three papers do not yet prove a causal link between infection with a specific virus and SD. The key study by Tzeng *et al.* [9] has also some limitations that we highlight below.

First, the paper does not present any comprehensive data on the exact numbers of patients in each category of dementia, but relies instead on relative risk factors, an omission that further reports from the investigators will need to address. Second, in European and North American populations the patient group presenting with acute HSV infection is strongly biased in favor of females, whereas in the Taiwan study group an excess of males was seen. There is no obvious explanation for this discrepancy, although it is possible that societal, environmental, and/or genetic differences might underlie this difference.

Third, the study group in Tzeng *et al.* [9] was selected by their susceptibility to severe overt HSV infection; equivalent studies on subpopulations susceptible to other types of infection would be valuable. Another study – a 10 year follow-up of patients with chronic peridontitis/gingivitis in the index year – did reveal a small trend towards an increased rate of SD in patients versus controls (1.13% versus 0.92%) [10], but focused examination of brain-related infections (for example, bacterial ~~conjunctivitis/~~encephalitis/meningitis, as well as viral encephalitis) could help to evaluate the relative proportions of SD cases that might be attributed to herpes viruses versus other infectious agents.

Fourth, the incidence of SD in the study group (acute HSV infection; n = 8362) represents a very small proportion of total SD cases. In a population of 24 million (Taiwan), making some assumptions regarding mean age and SD incidence in the general population, the calculated number of SD cases in this group would represent at most well under 1% of all SD cases in that country. In the absence of further data it is not possible to know whether viral infection might be a contributory factor to SD development more generally, or is likely to be responsible for only a minority of SD cases.

Fifth, these results are so far unreplicated. Findings in Taiwan may not be representative of other populations worldwide, and studies elsewhere will be essential for confirming or otherwise these data. Nonetheless, over 130 studies to date, using a variety of approaches, support a major role for HSV1 in AD; it is possible that the broad conclusions of the Taiwanese studies might also apply to the high proportion of individuals who, although HSV1-seropositive, have remained largely asymptomatic to date.

It must be stressed that these studies give no information about subjects who already suffer from SD: the data apply only to AVT in a small minority group applied well before any obvious symptoms of dementia. Although a clinical trial to evaluate the potential of AVT in early SD has been initiated [11], it will take several years before any results become available. The finding that AVT can prevent later SD development, albeit in a very small proportion of the population, does directly implicate herpes infection as a causal factor in at least some cases. Although the principle is now firmly established, its generality requires independent replication, and, importantly, the proportion of SD cases that might be attributed to virus infection remains unknown – and still might represent only a minority. Despite these important caveats, these three thought-provoking reports will undoubtedly stimulate further investigations into the link between infection and SD.

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