Alzheimer’s disease, herpes simplex virus type I, cold sores and apolipoprotein E4.

WOAN-RU LIN, DAZHUANG SHANG, G.K. WILCOCK* and RUTH F. ITZHAKI

Molecular Neurobiology Laboratory, Department of Optometry & Vision Sciences, UMIST, Manchester M60 1QD, U.K.

*Department of Care of the Elderly, Frenchay Hospital, Bristol BS16 1LE, U.K.

The majority of cases of Alzheimer’s disease (AD) are sporadic, and although an inherited risk factor has been discovered - the gene for the type 4 variant of apolipoprotein E (apoE) - it is neither essential nor sufficient to cause the disease. Environmental agents must presumably be involved also but there is no consensus about which are possible candidates [1]. One of the factors we have been investigating is herpes simplex virus type 1 (HSV1); this virus has been implicated as a possible factor because in acute HSV1 encephalitis, it affects the same regions of the brain as those most affected in AD, because of its ubiquity and because of its propensity for lying latent in neurones. In fact nearly all adults harbour HSV1 [2,3] in the peripheral nervous system (PNS) in a latent state, i.e., the genome is present but there is no production of virions nor of any (detectable) virus proteins. The virus reactivates periodically, and in certain people leads to occurrence of cold sores. As to whether or not HSV1 DNA is present in the central nervous system (CNS), there was complete uncertainty for many years owing to the use of relatively insensitive methods such as hybridisation for detecting nucleic acids, or immunocytochemistry for detecting viral proteins. However, in this laboratory we have used polymerase chain reaction (PCR) to search for HSV1 DNA in post mortem brain [4-6], taking extreme precautions against contamination of specimens or of DNA and PCR assay mixtures, and also against false positives. Our primers detect the latter is the region least affected in AD and the former three are those most affected. Reverse PCR assays indicated that it is present in brain specimens examined. If the results are substantiated, HSV1 would be implicated with 95% confidence intervals for the apoE4 allele of HSV1-positive ADs/HSV1-positive aged normals is three times greater than that of the total AD/total aged normals. In the HSV1-negative groups, the apoE4 frequencies of ADs and age-matched normals are similar. The results suggest that the combination of HSV1-positivity and possession of an apoE4 allele confers a greater risk of developing AD than does possession of the apoE4 allele alone. Alternative possibilities - that AD patients, or possessors of an apoE4 allele, are predisposed to HSV1 infection of the CNS - are unlikely since we have found HSV1 in the CNS of many of the age-matched normals, few of whom possess an E4 allele.

Fig. 2. ApoE4 frequency of (a) AD patients and age-matched normals who are HSV1-positive in brain; (b) cold sore sufferers and age-matched normals.

We decided to compare a host factor - the apoE genotypes of the AD patients and the age-matched normals. Fig. 2a shows the E4 allele frequency for those we found to be HSV1-positive in brain; the value for the ADs is very significantly greater than for the age-matched normals (p<0.001), and significantly greater than the reported frequency for ADs, which is about 31-35% (p<0.01). The odds ratio with 95% confidence intervals for the apoE4 allele of HSV1-positive ADs/HSV1-positive aged normals is three times greater than that of the total AD/total aged normals. In the HSV1-negative groups, the apoE4 frequencies of ADs and age-matched normals are similar. The results suggest that the combination of HSV1-positivity and possession of an apoE4 allele confers a greater risk of developing AD than does possession of the apoE4 allele alone. Alternative possibilities - that AD patients, or possessors of an apoE4 allele, are predisposed to HSV1 infection of the CNS - are unlikely since we have found HSV1 in the CNS of many of the age-matched normals, few of whom possess an E4 allele.

To find if, in the PNS also, the combination of possession of HSV1 and an E4 allele is damaging, we examined the apoE genotypes of 24 cold sore sufferers and 24 age-matched normals. We checked that the individuals had been exposed to the virus by examining the serum of 22 of the 24 sufferers and 22 of the non-sufferers. As expected, nearly all were seropositive for HSV; only one - a control - was seronegative. In support of our hypothesis, we found (Fig. 2b) that the apoE4 allele frequency of the cold sore group is in fact significantly greater than that of the age-matched normals (p<0.01). The distribution of alleles for the non-sufferers - and for the aged normals in the AD study - was as expected for controls.

We plan to extend these studies by increasing the numbers of specimens examined. If the results are substantiated, HSV1 would be implicated as a definite risk factor in AD - the first to be discovered - and the nature of the interaction between the inherited and the environmental factor would be investigated.

We thank the Sir Halley Stewart Trust for support of this work, Mestler-Toledo for a donation, Ms S. Matthews for skilled assistance to G.K.W., and Drs Brooke and Parker for taking blood samples.