Letters

Herpes simplex virus: a role in the aetiology of Alzheimers disease?

Sir: A Herpes simplex virus aetiology for Alzheimer's disease¹ offers an explanation for adult onset and the selectivity for temporal lobe.² However, serological studies^{3,4} have not shown a consistent increase in antibody titres to Herpes simplex virus. Although sparse Herpes simplex virus immunoreactivity has been reported in normal and in Alzheimer brain tissue,^{5,6} and there is report of Herpes simplex virus DNA in three out of four brain smears,⁷ the Herpes simplex virus hypothesis has not been confirmed in other larger DNA hybridisation studies.⁸⁻¹⁰ Even if Herpes simplex virus infection were present it is not clear that it could account for the selective pattern of neurochemical deficit (decrease in choline acetyl transferase,¹¹ reduction in 5HT² receptors¹² and somatostatin immunoreactivity^{13,14}) seen in cases of Alzheimer's disease. We have investigated an Herpes simplex virus aetiology for Alzheimer's disease using two approaches:—(1) a survey to look for the presence of Herpes simplex virus antigenicity (an active infection) in 25 cases of histologically diagnosed Alzheimer's disease and 32 non-neurological controls. (2) an investigation to determine if known cases of herpes encephalitis (human and a mouse model) produced a similar destruction of somatostatin-containing neurons in the temporal lobe to that seen in Alzheimer's disease.

For the first study brains were obtained post mortem and fixed in 10% formalin. Blocks of tissue containing temporal lobe structures were dissected out and embedded in paraffin. Sections 15 µm thick were cut and processed for immunocytochemistry using the PAP method and an anti-Herpes simplex virus antibody (DAKO, dilution 1:500). Additional sections were processed for absorption controls and a confirmed case of human Herpes simplex virus encephalitis was used as a positive control.

Abundant immunoreactivity was present in temporal lobe areas in the encephalitis case with large numbers of neurons and glia showing evidence of active infection. No Herpes simplex virus antigenicity was seen in any temporal lobe area in the Alzheimer's disease cases or the controls.

For the second study material from the Herpes simplex virus encephalitis case and from mice infected intracranially 3 days previously with Herpes simplex virus were pro-

cessed in the same fashion as above (formalin fixation, paraffin embedding, immunocytochemistry) and stained with a number of antisera to different peptides: somatostatin, CCK, VIP etc. These studies showed that the damage caused by Herpes simplex virus infection was extensive, and loss of immunoreactivity was found for each of the peptides studied. This contrasts with the selective depletion, previously reported, of somatostatin immunoreactivity in Alzheimer's disease.¹³

The absence of significant Herpes simplex virus immunoreactivity in Alzheimer's disease and our failure to detect Herpes simplex virus DNA⁹ (subsequently replicated¹⁰) taken together with the general depletions in peptide immunoreactivity and recent reports that the depletion in CAT activity¹¹ and 5HT² receptor number¹² found in Alzheimer's disease are not found in Herpes simplex virus infected mice¹⁵ make it unlikely that Herpes simplex virus has any role in the aetiology of Alzheimer's disease.

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References

- ¹ Ball MJ. Limbic predilection in Alzheimer Dementia: is reactivated Herpes virus involved? *Can J Neurol Sci* 1982;9:303-6.
- ² Damasio AR, Van Hoesen GW. The limbic system and the localisation of Herpes simplex encephalitis. *J Neurol Neurosurg Psychiatry* 1985;48:297-301.
- ³ Whalley CJ, Urbaniak SJ, Darg C, et al. Histocompatibility antigens and antibodies to viral and other antigens in Alzheimers presenile dementia. *Acta psychiat Scand* 1980;61:1-7.
- ⁴ Renvoize EB, Hambling MH. Cytomegalovirus infection and Alzheimers disease. *Age Ageing* 1985;14:205-9.
- ⁵ Esiri MM. Viruses and Alzheimers disease. *J Neurol Neurosurg Psychiatry* 1982;45:759.
- ⁶ Mann DMA, Tinkler AM, Yates PO. Neurological disease and Herpes simplex virus. *Acta Neuropathol (Berl)* 1983;60:24-8.
- ⁷ Sequiera LW, Jennings LC, Carrasco LH, et al. Detection of Herpes simplex viral genome in brain tissue. *Lancet* 1979;2:609-12.

- ⁸ Middleton PJ, Petric M, Kozak M, et al. Herpes simplex viral genome and senile and presenile dementias of Alzheimer and Pick. *Lancet* 1980;1:1038.
- ⁹ Taylor GR, Crow TJ, Markakis DA, et al. Herpes simplex and Alzheimers disease: a search for virus DNA by spot hybridisation. *J Neurol Neurosurg Psychiatry* 1984;47:1061-5.
- ¹⁰ Pogo BGT, Elizan TS. Search for viral DNA sequences in Alzheimer brain tissue. *Lancet* 1985;1:978.
- ¹¹ McGeer PL. Ageing, Alzheimers disease and the cholinergic system. *Can J Physiol Pharmacol* 1984;62:741-54.
- ¹² Cross AJ, Crow TJ, Ferrier IN, et al. Serotonin receptor changes in dementia of the Alzheimer type. *J Neurochem* 1984;43:1574-81.
- ¹³ Roberts GW, Cross TJ, Polak JM. Location of neuronal tangles in somatostatin neurones in Alzheimers disease. *Nature* 1985;314:92-4.
- ¹⁴ Joynt RJ, McNeil TH. Neuropeptides in ageing and dementia. *Peptides (Fayetteville)* 1984;5 supplement 1:269-74.
- ¹⁵ Cross AJ, Crow TJ, Johnsson JA, et al. Effects of experimental herpes simplex virus (HSV) encephalitis on monoamine systems in mouse brain. *J Physiol (Lond)* 1980;350:30P.

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Legionella brainstem encephalopathy and peripheral neuropathy without preceding pneumonia

Sir: Neurological manifestations of legionella infection are diverse, commonly involving encephalopathy¹ and less frequently brainstem encephalopathy,² cerebellar dysfunction,³ cranial nerve involvement,⁴ myelopathy^{5,6} and peripheral neuropathy.⁷ Diagnosis of the cause of the neurological deficit usually depends upon the recognition of a preceding atypical pneumonia, with subsequent serological confirmation. However, legionellosis is a multisystem disease with variable abdominal, renal and haematological manifestations; pulmonary involvement may be slight or absent.⁸⁻¹⁰ We describe a patient with severe brainstem encephalopathy in whom diarrhoea was the only prodromal feature of legionella infection.

A 49-year-old woman experienced diarrhoea for a week, followed by a rapidly progressive neurological deficit. She had familial pes cavus without significant disability and had been able to run and dance. She had been otherwise fit. She was admitted two days after developing progressive drowsiness, diplopia, dysarthria, dysphagia, unsteadiness and peripheral paraesthesiae.