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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Accepted 6 July 1985

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.

General examination was normal; she was apyrexial and there was no neck stiffness. She was drowsy with bilateral grasp reflexes. Eye movements were restricted in all directions. Pupils were large and only slightly reacted to light. There was bilateral facial weakness and dysarthria. She had bilateral pes cavus, generalised weakness of her legs, absent tendon reflexes and flexor plantar responses. There was a distal sensory loss to light touch and pin-prick and generalised incoordination. Investigations revealed: blood leucocyte count $17,000/\text{mm}^3$ (7% lymphocytes), sedimentation rate 37 mm in the first hour; haemoglobin, serum urea, electrolytes, glucose, electrocardiogram, skull and chest radiographs, and CT brain scan were normal. Cerebrospinal fluid (CSF) was at normal pressure and contained less than 2 lymphocytes/ mm^3 ; cytospin examination revealed normal lymphocytes. Gram and Ziehl-Nielsen stains were negative, protein 950 mg/l and glucose 4.0 mmol/l. As *Herpes simplex* encephalitis was a possibility she was treated with intravenous acyclovir 10 mg/kg tds for 10 days, but the presence of progressive neuropathy raised the possibility of an unusual manifestation of legionellosis.

Three days following admission, brainstem function had deteriorated further and the CSF taken on admission exhibited a cytotoxic effect on MRC-5 cell culture (not repeatable on passage). As *Legionella pneumophila* is known to produce several toxins, including a cytotoxin,¹¹ IV erythromycin (1g qds) was started. Allergy to erythromycin, and preference for rifampicin in CNS involvement with legionella¹ prompted substitution at 5 days by IV rifampicin 600 mg bd, together with intramuscular tetracycline, 100 mg qds, for 16 days. Six days following admission she was unconscious with fixed mid-point pupils, unresponsive to pain, and mechanically ventilated. No brainstem reflexes could be elicited, although caloric testing was not performed. Thereafter, she improved gradually; by ten days she breathed spontaneously and extended limbs to pain; at 3 months she was ambulant and returned home.

Further investigations confirmed the diagnosis of legionellosis; serum antibody titres to *Legionella pneumophila*, taken on days 2 and 14, rose from 1/64 to 1/1024 (rapid microagglutination test, RMAT) and from 1/256 to 1/512 (IgM—direct fluorescent antibody test, IFAT).¹² CSF, six days after admission contained 1 lymphocyte/ mm^3 , protein 1650 mg/l and glucose 4.5 mmol/l. CSF: serum albumen ratio suggested blood brain barrier breakdown but the IgG index indicated no significant CNS IgG/synthesis,

nor were oligoclonal bands demonstrated. Antibodies to legionella were undetectable in CSF taken at 6 and 16 days. CSF culture for bacteria (including listeria and *Mycobacterium tuberculosis*) and fungi were negative. Special media to culture legionella were unavailable. The cytotoxic effect was not demonstrable in CSF collected at 6 days. Serum and CSF titres to Epstein-Barr virus, *Herpes simplex*, adenovirus, mumps and mycoplasma did not rise significantly. Toxoplasma and syphilis serology and urinary porphyrins were negative. Plasma sodium was always above 130 mmol/l. Liver and renal function and creatine kinase (CK) remained normal. Chest radiographs never showed significant consolidation. Neurophysiological investigations at 6 days revealed a severe demyelinating sensorimotor polyneuropathy with median and ulnar nerve conduction velocities of 14 and 18 m/s respectively. Brainstem auditory evoked potentials (BAEPs) were delayed, but never absent.

Six months later she had improved considerably. Mental function and cranial nerves were normal. Sensation was slightly blunted in hands and feet. Her arms were otherwise normal, but walking was limited to about 350 m. Examination revealed impairment of upgaze, distal sensory impairment to light touch and pin-prick, distal weakness and wasting (particularly of peoneal muscles), areflexia and truncal ataxia. Nerve conduction velocities remained low, but BAEPs were normal.

Legionellosis may present with neurological dysfunction, and paucity of systemic features does not preclude the diagnosis; occasional reported cases have had neurological deficits without pneumonia^{5,6,13} although, to our knowledge, none has presented with such severe, focal, brainstem involvement. A mild peripheral neuropathy may partly have antedated this illness, although this was not symptomatic. The diagnosis of legionellosis is supported in our case by the presence of diarrhoea (which occurs in 50% of patients with legionellosis¹⁴) and strongly positive serological tests, despite the absence of common systemic features such as pneumonia, myalgia, pyrexia, hyponatraemia, liver or renal dysfunction, or raised CK. The RMAT and IFAT (using formalised yolk sac antigen) show excellent specificities, without known cross-reactivity.¹²

As legionella antigen has been demonstrated in extrapulmonary sites, including the brain, using immunofluorescent techniques,¹⁵ it has been suggested that direct bacterial invasion causes the neurological

deficit. Neuropathological examination generally has failed to demonstrate bacilli or histological lesions attributable to invasion of the central nervous system by legionella,^{16,17} although two cases have been reported in which characteristic bacilli were seen in the brain, in one instance associated with severe combined immuno-deficiency.^{18,19} It has been suggested that the neurological deficit is caused by a toxin,¹⁸ and an "endotoxin"²⁰ and cytotoxin^{11,21} have been detected in association with legionella. The cytotoxic effect of CSF collected early in our patient's illness and its subsequent disappearance, are compatible with this hypothesis. The absence of antibody to legionella in the CSF and the lack of local IgG production favour a neurotoxin-mediated effect rather than direct a bacterial invasion, as does the often noted absence of a cellular response in the CSF.^{23,58,16}

Rational treatment of patients with neurological involvement due to legionellosis must await clarification of the part played by direct invasion of the nervous tissue by legionella bacillus, as opposed to the effect of toxin in the production of neurological damage. If persistence of bacteria is important for the evolution of neurological damage (due either to direct invasion or continued toxin production), then early antibiotic treatment may be advantageous. Rifampicin is more likely to exceed the minimum inhibitory concentration for legionella in the CSF than erythromycin, especially if there is breakdown of the blood brain barrier.²² However, rifampicin should not be given alone, as resistance may develop. If bacterial eradication has occurred leaving an active toxin, then treatment directed towards toxin neutralisation may be appropriate, although the half-life of the toxin may be short. Until these uncertainties are resolved, early antibiotic treatment, including rifampicin, appears reasonable and should be considered where the neurological presentation alone suggests that legionella infection may be responsible.

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Accepted 10 May 1985

Lateral sinus thrombosis and intracranial hypertension in essential thrombocythaemia

Sir: Essential thrombocythaemia can be associated with arterial and venous thrombosis.¹ The association with lateral sinus thrombosis and intracranial hypertension has not previously been described in this disease. We report such a case in a patient who also had evidence of portal vein thrombosis.

A 31-year-old man presented with intermittent epigastric pain. Marked splenomegaly and a microcytic hypochromic anaemia with a haemoglobin of 10 g% were noted. Bone marrow examination suggested early myeloproliferative disease. Eight months later he had a haematemesis and endoscopy showed oesophageal varices. White cell count then was $5.0 \times 10^9/l$ with normal differential and a platelet count of $442 \times 10^9/l$. An ultrasound examination of the liver showed a highly echogenic area in the region of the porta hepatis. CT scan of the abdomen showed gross splenomegaly and the portal vein did not increase in density after contrast injection supporting a diagnosis of portal vein thrombosis. Four months later, during an admission for injection of oesophageal varices he developed diarrhoea and vomiting. Salmonella was isolated and he was treated with ampicillin and metronidazole. Seven days later he complained of an initially predominantly right sided headache and photophobia. Neurological examination was normal. A CT scan of the brain with enhancement was normal. A lumbar puncture in the recumbent position showed a CSF pressure of 25 cm of H_2O (normal up to 18 cm of H_2O), normal protein, cell content and glucose. At this time his platelet count which had been persistently over $500 \times 10^9/ml$ had reached $792 \times 10^9/ml$. Generalised headaches increased by cough persisted and further lumbar punctures over the ensuing two months showed pressures of 28 and 24 cm of H_2O . After each of these the headache was temporarily relieved. During this time he was treated

Fig Lateral oblique view of the skull during digital subtraction angiography (intravenous study). The arrows indicate a clot shown as a filling defect within the left lateral sinus.

with acetazolamide. Digital subtraction angiography with intravenous injection of contrast showed adequate filling of arterial cerebral vessels but a filling defect due to a thrombus in the left lateral sinus (fig). A further bone marrow aspirate and trephine showed active haemopoiesis with increased megakaryocytes and increased reticulin stain. The appearances were considered characteristic of essential thrombocythaemia (Prof J Barrett). A single dose of 50 mg oral busulphan was administered. The platelet count has remained between 150 and $300 \times 10^9/ml$ and no recurrence of his symptoms has been observed for three months.

The two venous thromboses within a year were probably secondary to essential thrombocythaemia. One previously reported case of intracranial hypertension in this condition was interpreted as "benign" or "pseudotumour cerebri".² Other recorded neurological complications include stroke, transient ischaemic attacks, confusional states, migraine, epilepsy, polyneuritis and radiculomyelopathy.³⁻⁵ We suggest that the lateral sinus thrombosis shown by digital subtraction angiography was the cause of the observed intracranial hypertension. Dehydration may have also been involved in the pathogenesis of this thrombosis as vomiting