Letters

Table

	Control Means $\pm$ SEM (n)	Alzheimer's disease Means $\pm$ SEM (n)	p (ANOVA)
Occipital cortex	22.5 $\pm$ 3.6 (6)	9.0 $\pm$ 2.0 (5)	< 0.02
Parietal cortex	20.1 $\pm$ 3.0 (6)	8.8 $\pm$ 2.3 (6)	< 0.02
Frontal cortex	32.1 $\pm$ 5.5 (7)	11.4 $\pm$ 1.9 (5)	< 0.02
Temporal cortex	27.1 $\pm$ 4.9 (7)	8.3 $\pm$ 2.0 (7)	< 0.02
Hippocampus	17.8 $\pm$ 7.8 (5)	6.0 $\pm$ 2.0 (7)	< 0.05
Caudate	14.5 $\pm$ 3.0 (6)	8.0 $\pm$ 3.4 (4)	NS
Globus pallidus	10.3 $\pm$ 4.8 (4)	10.2 $\pm$ 4.2 (3)	NS
Putamen	13.2 $\pm$ 2.5 (5)	8.4 $\pm$ 5.0 (2)	NS

We interpret these results as indicating a severe (60%) loss of glutamate terminals in cortical and hippocampal regions in Alzheimer's disease with little or no loss of glutamate innervation in subcortical regions. These results suggest a large glutamatergic deficit in Alzheimer's disease consistent with the pathology of the disorder.¹

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Glutamate deficits in Alzheimer's disease

Sir: The presence of large numbers of senile plaques and neurofibrillary tangles in cerebral cortex is the major neuropathological feature of Alzheimer-type dementia (ATD).¹ It has recently become clear that cortical neurofibrillary tangles are present predominantly in pyramidal neurons,² and that these neurons may degenerate in ATD.³ Studies in experimental animals suggest that cortical pyramidal neurons use an excitatory amino acid such as glutamate as transmitter, and there is much current interest in the study of excitatory amino acids in ATD. Direct study of glutamate-containing neurons in human brain have been hampered by the lack of a suitable marker. We have recently shown that the binding of ³H-D-aspartate to the high-affinity glutamate uptake site may be a useful marker of glutamate-containing nerve terminals in human post-mortem brain.⁴ We report here a study of ³H-D-aspartate binding in cortex of controls and ATD patients.

Brains from controls and neuropathologically confirmed ATD patients

were obtained at necropsy, snap-frozen and 20 μ m cryostat-cut sections of temporal cortex collected. The groups were matched for age and post-mortem delay (table). The binding of ³H-D-aspartate to slide-mounted tissue sections was performed as described previously.^{4,5} Sections were incubated for 30 min with 100 nM ³H-D-aspartate in 50 mM Tris acetate buffer pH 7.4 containing 100 mM NaCl. After incubation, the sections were washed and the tissue scraped into vials for scintillation counting.

We observed a pronounced and significant decrease in ³H-D-aspartate binding in the ATD group (table). This decrease is unlikely to be due to factors associated with chronic neuropsychiatric diseases such as hypoxia, as we find no loss of ³H-D-aspartate binding in cortex of Huntington's disease patients.⁶ ³H-D-aspartate binding in frontal cortex of controls; 426 $\pm$ 96 fmol/mg (n = 8) and Huntington's disease patients 418 $\pm$ 148 fmol/mg (n = 10). Moreover, the groups used in the present study were matched for age and post-mortem delay.

The results are consistent with a loss of cortical glutamate-containing nerve terminals, and may thus provide a neurochemical correlate of changes in pyramidal neurons in ATD. In a previous study, glutamate release from cortical tissue prisms was shown not to be reduced in ATD,⁷ suggesting that glutamate terminals may remain intact. However, it has recently been suggested that glutamate release may be more directly linked to changes in metabolic activity than to changes in glutamate containing terminals.⁸

The small number of patients in the present study necessitates confirmation of this finding in a larger group of patients. If confirmed, the present results suggest that ³H-D-aspartate may be a useful means to study the progression of pathological

Table Post-mortem details and ³H-D-aspartate binding in controls and ATD patients

	Controls n = 5	ATD patients n = 5
Age (y)	68 $\pm$ 7	72 $\pm$ 6
Post-mortem delay (h)	36 $\pm$ 10	38 $\pm$ 14
³ H-D-aspartate binding (fmol/mg)	184 $\pm$ 16	98 $\pm$ 26*

*p < 0.05.

change postulated to occur in cortical neurons in ATD.²

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Primary cerebral lymphoma mimicking tuberculosis: case report

Sir: A 19 year old Chinese man presented to another hospital having suffered a generalised convulsion. He was previously well other than a one year history of weight loss, and had been fully immunised as a child, including BCG, at age 9 years. Examination at this time showed him to be unwell, but the only physical signs were pyrexia of 37.8°C,

mild neck stiffness and photophobia. A full blood count showed a white cell count of $14.2 \times 10^9/l$ with a 61% lymphocytosis. A diagnosis of viral meningitis was made and a lumbar puncture performed which showed an opening pressure of 20 cm water, and CSF which contained 40 wbc/mm³ (98% lymphocytes), protein 0.4 g/l, glucose 2.6 mmol/l (blood glucose 5.0 mmol/l), cytology and Gram-stain negative. In view of the convulsion he was started on phenytoin and was transferred to the regional Neurological unit at the Royal Surrey County Hospital.

On admission to this hospital he was drowsy but orientated and gave a coherent history. There were no focal signs. Investigations included: FBC, ESR, urea and electrolytes, liver function tests, calcium, protein electrophoresis, immunoglobulins, glucose, autoimmune profile, angiotensin converting enzyme, viral titres, syphilis serology, toxoplasma dye test, CSF Gram stain, CSF and serum cryptococcal antigens, CSF india-ink preparations, CSF oligoclonal study, CSF latex agglutination test for tuberculosis, tuberculin test, ECG, chest and skull radiographs, upper gastrointestinal endoscopy, abdominal ultrasound, barium enema, Kveim test, stool, urine, CSF and blood cultures, bone marrow examination and 24 hour urinary calcium, all of which were either normal or negative.

A CT brain scan was performed which showed multiple enhancing lesions with contrast enhancement of the adjacent cortical folds suggesting meningeal involvement. The right frontal lesion showed oedematous characteristics but notably a densely enhancing nodule at the junction of the cortex and white matter said to be typical of a granulomatous process with tuberculosis being the most likely cause (fig. a). Quadruple therapy with isoniazid, rifampicin, ethambutol and streptomycin was therefore commenced. One week later the patient became acutely unwell with fever, generalised rash and severe oro-pharyngeal ulceration. A "septic screen" was negative and his condition was attributed to a drug reaction to either phenytoin or the anti-tuberculous drugs. All medication was stopped and intravenous hydrocortisone given and his fever and rash settled. A repeat CT brain scan (fig. b) was performed 10 days after starting steroid therapy and showed virtual resolution of the multiple lesions seen previously. Quadruple therapy was then reintroduced and the steroid therapy reduced to a maintenance dose of cortisone acetate 25 mg tds. He suffered no further drug reaction.

His condition remained stable over the next 2 weeks but a further CT brain scan showed a new large, well circumscribed lesion in the right frontal area with surrounding oedema (fig. c). In view of the rapid occurrence of new cerebral lesions while on anti-tuberculous therapy, it was felt that a histological diagnosis was required. The patient was therefore transferred to Atkinson Morley's Hospital, London where he underwent a right frontal craniotomy and biopsy of the right frontal lesion. Histology was reported as showing a perivascular exudate of lymphocytes and larger reticulo-endothelial cells which did not appear neoplastic. The appearances were essentially non-specific but could be compatible with tuberculosis.

After operation he remained drowsy and clinically unchanged, but over the next weeks progressively deteriorated developing left-sided 6th, 7th, 9th and 10th cranial nerve palsies and tetraplegia. He died 6 months after presentation.

It was only possible to secure permission from the relatives for a limited necropsy confined to the brain, and this showed diffuse cerebral lymphoma of the histiocytic type, with deposits in the brain-stem, cerebellum, and hemispheres (fig. d). Systemic lymphoma cannot, therefore, be completely excluded, but investigations in the early stages of the illness would suggest that this was a primary cerebral lymphoma.

This case is presented because of the diagnostic problems it posed, because of the way in which cerebral lymphoma mimicked cerebral tuberculosis, and to emphasise how cerebral lymphoma lesions may regress with steroid therapy. The patient presented with progressive meningoencephalitis and the initial CSF findings of a lymphocytic pleocytosis with normal protein, glucose and negative Gram stain and culture were compatible with this diagnosis. However CT scanning at an early stage revealed the more diffuse nature of the condition with parenchymal involvement of at least four cerebral lobes.

Our case was complicated by a severe drug reaction, but in retrospect it was thought probable that it was the use of steroids to treat this reaction that led to regression of the lesions.

Tuberculosis was considered to be the most likely diagnosis and since early treatment is essential (the disease usually being fatal in 4 to 6 weeks in untreated cases) anti-tuberculous therapy was started. The normal CSF glucose and protein levels are unusual but not incompatible with the diagnosis.¹ Acid-fast bacilli are seen in only 40% cases on initial CSF examination,² and the tuberculin test is negative in 50% cases at