Cerebrospinal fluid tau concentrations in HIV infected patients with suspected neurological disease

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Objectives: To measure cerebrospinal fluid (CSF) tau in HIV infected patients with acute neurological episodes and to correlate the findings with the type and severity of neurological disease.

Methods: CSF tau was prospectively measured in 76 consecutive HIV infected patients admitted to a specialist unit at UCL Hospitals, London, for investigation of acute neurological episodes: the results were compared with the clinical diagnoses.

Results: 24 patients had HIV associated dementia complex (HADC), 10 had lymphoma (including four with primary CNS lymphoma), 20 had cerebral infections (including five with CMV encephalitis, five with VZV infection, seven with cryptococcal meningitis, two with toxoplasmosis, and one with progressive multifocal leucoencephalopathy); 22 patients had miscellaneous conditions, including nine with self limiting headache/fever. 62 patients (82%) had normal CSF tau concentration and 14 patients (18%) had elevated tau. In those with HADC, there was no correlation between the degree of dementia or atrophy on magnetic resonance imaging and CSF tau. Elevated CSF tau was associated with poor outcome as six of eight patients who died within 4 weeks of lumbar puncture had elevated tau (p=0.0024, two tailed Fisher’s exact test).

Conclusions: CSF tau levels are not elevated in the majority of HIV infected patients presenting with acute neurological episodes. CSF tau levels show no correlation with severity of dementia/atrophy on magnetic resonance imaging. Although elevated CSF tau was observed in some patients with conditions causing cerebral necrosis, the finding did not delineate underlying pathology but was associated with poor outcome.

Keywords: tau; AIDS; cerebrospinal fluid; dementia; magnetic resonance imaging

Introduction

Tau protein is a microtubule associated phosphoprotein which promotes microtubule assembly and stabilisation. It is found in high concentrations within axons of the central nervous system and elevated concentrations of tau may be detected in cerebrospinal fluid of patients with neuronal damage due to acute ischaemic stroke and Creutzfeldt-Jakob disease. CSF tau concentrations are also elevated in patients with Alzheimer’s disease and frontotemporal dementia. Elevated tau is thought to be related to neuronal loss, which occurs in these conditions. By contrast elevations of CSF tau are not seen in all neurodegenerative disorders—for example, Parkinson’s disease, but this may simply reflect the extent and rate of neurodegeneration.

Clinically apparent neurological dysfunction occurs in up to 40% of patients with AIDS, and at necropsy, over 75% have abnormalities of the central nervous system. Cerebral infection with HIV itself produces a subacute dementia known as HIV associated dementia complex (HADC). Neuropathological changes associated with HADC include a giant cell encephalitis, leucoencephalopathy with myelin pallor, astrogliosis, and neuronal loss. HIV viral load, macrophage activation markers and tumour necrosis factor α (TNF-α) levels in the brain correlate with the presence and severity of dementia whereas cortical neuronal counts do not. Tangle-like structures showing immunoreactivity to tau have been described in brains of HIV infected patients, yet measurements of tau in CSF of this patient group have shown conflicting results. In one study CSF tau levels were normal in 32 HIV positive patients who were either neurologically asymptomatic or had neurocognitive disorders or peripheral neuropathy. By contrast, CSF tau was elevated in three of four HIV infected patients with unspecified neurological diagnoses. In this prospective study we measured CSF tau in consecutive HIV positive patients undergoing diagnostic lumbar puncture for investigation of suspected neurological disease. In those with HADC we attempted to correlate CSF tau measurements with the clinical severity of dementia, and as a marker of neuronal loss, the degree of atrophy on cranial magnetic resonance imaging.

Methods

We prospectively studied 76 consecutive HIV-1 antibody positive patients admitted to a specialist HIV/AIDS inpatient unit at University College Hospitals (Middlesex Hospital site) for investigation of neurological episodes.
The study was carried out within the guidelines of the Middlesex Hospital clinical investigations panel.

The patients were aged 26–72 years (median 37 years). Sixty two patients were males (58 white homosexuals, four African homosexuals) and 14 were females (11 African and three white), 13 of whom were heterosexuals and one whose risk factor was a “needlestick” injury. As a group the patients were profoundly immunosuppressed with CD4 + T lymphocyte counts ranging from 0 to 440 cells \times 10^6/l (median 40 cells \times 10^6/l, normal range 250–1200 cells \times 10^6/l). All but seven patients had CD4 + T lymphocyte counts \leq 250 cells \times 10^6/l.

All patients were under the care of a specialist HIV physician. They were investigated using a unit protocol. Following clinical assessment and computed tomography (CT) and/or magnetic resonance imaging (MRI) of the brain, lumbar puncture was carried out. In addition to routine biochemical analyses, CSF was stained histochemically with Gram’s stain, auramine, Grocott’s methenamine silver, India ink, and mucicarmine and cultured for bacteria, mycobacteria, and fungi. Assays for cryptococcal antigen and tests for antibodies to Treponema pallidum and Toxoplasma gondii were carried out. CSF was also analysed by nested polymerase chain reaction (nPCR) for presence of cytomegalovirus (CMV), varicella zoster virus (VZV), herpes simplex virus type-1 and type-2, Epstein–Barr virus and JC virus as previously described.10 An aliquot of CSF (250 µl) was frozen immediately at −20°C and stored for subsequent tau measurement. A diagnosis of HADC was made on the basis of presentation with a subacute onset, with at least 1 month of cognitive deficit with decline in motivation, emotional control, or change in social behaviour in the absence of clouding of consciousness,11 and in addition the absence of demonstrable infection of the CSF by staining, culture, and nPCR. The clinical severity of the cognitive deficit was recorded using the Memorial Sloan-Kettering criteria.12 Cranial MR images of those with HADC were re-reported, mixed in with scans from patients matched for CD4+ T lymphocyte count who had also presented with neurological symptoms and signs including HADC, by a radiologist (MH-C) experienced in the interpreting of cranial MR images of patients with HIV infection. The radiologist was blinded to the subjects’ clinical diagnoses and also did not know which were included in the tau protein study. Predetermined criteria were used to report the MR images; the degree of atrophy (graded none, mild, moderate, or severe) was recorded as previously described.10 13

CSF samples, frozen at −20°C, were transferred to the Institute of Neurology for analysis. CSF samples were coded and all analyses were performed blinded to the clinical diagnosis. CSF tau levels were determined using the Innotest human tau antigen second generation sandwich enzyme linked immunosorbent assay (ELISA) (Immunogenetics, Ghent, Belgium).14 The assay’s upper limit of normal in CSF is 315 pg/ml and has a lower limit of detection of 75 pg/ml.

### STATISTICAL ANALYSES

Multiple comparisons of normally distributed continuous variables were compared using a one way analysis of variance with post hoc Bonferroni analysis. Non-parametric data were compared using a two tailed Fisher exact test. A p value of < 0.05 was considered statistically significant.

### Results

Twenty four patients had HADC, 10 had B cell lymphoma, four had primary CNS lymphoma, and six had systemic lymphoma and were undergoing staging investigations. Six of these patients had cerebral lymphoma. Twenty patients had cerebral infections, including five with CMV encephalitis, five with VZV encephalitis, one had meningococcal meningitis, one had nercotising herpetic retinopathy, and one had an isolated third nerve palsy, seven with cryptococcal meningitis, two with cerebral toxoplasmosis, and one with progressive multifocal leucoencephalopathy. Twenty two patients had miscellaneous conditions, including nine with self limiting headache with fever, three with isolated grand mal fits, two with hysterical paraparesis, and eight had a variety of conditions including a single case each of strabismus, chronic demyelinating polyneuropathy, acute confusional state, central pontine myelinolysis, peripheral neuropathy, weight loss without apparent cause, urethral stricture, and paranasal sinusitis.

Measurements of CSF tau (mean (SD)) were similar in patients with HADC = 212 (180) pg/ml, lymphoma = 135 (84) pg/ml; cerebral infections = 265 (200) pg/ml, and miscellaneous conditions = 143 (72) pg/ml; p = NS (fig 1). Sixty two patients had normal concentrations of tau in CSF (fig 1) and 14 had elevated concentrations. The diagnosis, treatment, and outcome of those patients with elevated CSF tau concentrations are given in table 1.

In those patients with HADC, the clinical severity of dementia was mild in 15 patients,
In conclusion, CSF tau levels were not elevated in the majority of HIV infected patients presenting with acute neurological episodes. In those with HADC, there was no correlation between CSF tau and the degree of dementia or atrophy on magnetic resonance imaging. Although elevated CSF tau was observed in some patients with conditions associated with cerebral necrosis, this finding did not delineate underlying pathology but was associated with a poor outcome.

We thank Professor MJG Harrison for helpful discussion, Drs I G Williams and A Zuma for allowing us to study their patients, and Louise Hinds for typing the manuscript.

Contributors: All authors contributed to the design of the study, to data collection and analysis, and to writing drafts of the manuscript. AJBG performed the tau analyses; MAHC reported the MR images; RFM collated clinical, neurochemical and imaging data; EJT and GG interpreted the tau measurements. The original research proposal was put forward by EJT, AJBG, and RFM.

Conflict of interest: None.

Source of funding: Nil.

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