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article

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.

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Introduction

Tau protein is a microtubule associated phosphoprotein which promotes microtubule assembly and stabilisation.¹ It is found in high concentrations within axons of the central nervous system¹ and elevated concentrations of tau may be detected in cerebrospinal fluid of patients with neuronal damage due to acute ischaemic stroke² and Creutzfeldt–Jakob disease.^{2,3} CSF tau concentrations are also elevated in patients with Alzheimer's disease⁴ and frontotemporal dementia.⁵ 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 dementia⁶ whereas cortical neuronal counts do not.⁷ Tangle-like structures showing immunoreactivity to tau have been described in brains of HIV infected patients,⁸ 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.⁹ By contrast, CSF tau was elevated in three of four HIV infected patients with unspecified neurological diagnoses.² 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 heterosexuals) 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 ≤ 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 μ l) 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 Innostest human tau antigen second generation sandwich enzyme linked immunosorbent assay (ELISA) (Immuno-genetics, 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.¹⁵

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 (two of these patients had cerebral lymphoma), 20 patients had cerebral infections, including five with CMV encephalitis, five with VZV (three had meningoencephalitis, one had necrotising 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; $p = \text{NS}$ (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,

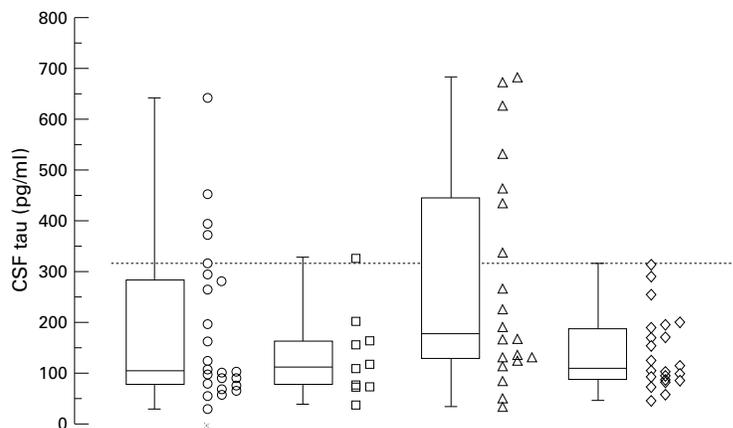


Figure 1 Combined scatter and box and whisker plots of CSF concentrations of tau in patients with HIV associated dementia complex (○) lymphoma (□) CNS infections (△) and miscellaneous conditions (◇). The boxes represent the 25th–75th quartile, divided horizontally by the median. The whiskers represent the range and the adjacent scatter plots represent the individual values from which the boxes and whiskers are derived. The horizontal broken line represents the upper limits of normal (315 pg/ml).

Table 1 Diagnosis, interventions, and outcome in HIV infected patients with elevated CSF tau

Diagnosis	CSF tau (pg/ml)	Intervention	Outcome and survival
HADC	316	None	Alive, >12 months
HADC	373	HAART	Alive, >9 months
HADC	396	HAART	Alive, >12 months
HADC	452	None	Died, <1 month
HADC	641	None	Died, <1 month
Disseminated extraneural NHL	328	Chemotherapy	Died, <1 month
CMV encephalitis	530	Ganciclovir	Died, <1 month
CMV encephalitis	629	Ganciclovir	Died, <1 month
Necrotising herpetic retinopathy (VZV)	437	Aciclovir, cidofovir, foscarnet	Alive, >12 months
VSV meningoencephalitis	336	Aciclovir	Alive, >12 months
PML	682	HAART	Alive, >15 months
Cerebral toxoplasmosis	673	Sulphadiazine/pyrimethamine	Alive, >6 months
Cryptococcal meningitis	466	Amphotericin/flucytosine	Died, <1 month
Isolated grand mal seizure	316	None	Alive, >12 months

HADC = HIV associated dementia complex; PML = progressive multifocal leucoencephalopathy; VZV = varicella zoster virus; CMV = cytomegalovirus; NHL = B cell non-Hodgkin's lymphoma; HAART = highly active antiretroviral therapy.

moderate in six patients, and severe in three patients. Cranial MRI showed atrophy was mild in 12 patients, moderate in five patients, and severe in two patients; five patients had no atrophy. An elevated CSF tau was found in five patients with HADC (table 1). Of these patients three had mild dementia/atrophy, one had moderate dementia/atrophy, and one had severe dementia/atrophy. There was no correlation between the clinical severity of dementia or the degree of atrophy on MRI and the concentration of tau in CSF.

Eight patients died within 4 weeks of lumbar puncture and CSF tau measurement; six of these patients had an elevated CSF tau (table 1) $p = 0.0024$, two tailed Fisher exact test. Of the eight who died, two with a diagnosis of disseminated lymphoma and normal CSF tau values underwent necropsy which confirmed the antemortem diagnosis. Irrespective of their diagnoses, there was no significant correlation between CD4 +T lymphocyte counts and concentrations of tau in CSF ($r^2 = 0.033$, $p = 0.11$).

Discussion

In this study we sought to measure CSF tau in consecutive HIV infected patients undergoing investigation for possible neurological disease. There were three striking findings in the present study. Firstly was the observation that CSF tau was not elevated in the majority (62/76) (82%) of patients, regardless of their CD4 lymphocyte count and their clinical diagnoses. These data suggest no role for measurement of CSF tau in the diagnosis of HIV infected patients with neurological episodes. These data are similar to those from a smaller study of 32 HIV infected patients of whom nine had HIV associated minor cognitive motor disorder or HADC and 23 were neurologically asymptomatic⁹: CSF tau was normal in 30/32 (93%) patients.

The second striking finding in our study was that although 5/24 of those with HADC had elevated CSF levels of tau, there was no correlation between the tau levels and the degree of clinical dementia or atrophy on magnetic resonance imaging. This suggests that CSF tau is a marker of acute neurodestruction and is unlikely to be useful as a marker of chronic low grade neurodestruction in which axonal dam-

age¹⁶ and subsequent release of tau is too low to be detected above the baseline. CSF tau may also be a bulk marker—that is, it is released in proportion to axonal bulk. Thus CSF tau levels may be low in patients with significant axonal loss, provided there is no superimposed acute axonal injury. This may explain the normal CSF tau values in patients with HADC and severe atrophy in whom there is active or ongoing neuroaxonal loss. A simple analogy would be the skeletal muscle isoform of creatine kinase, which is released in proportion to muscle bulk. However, when there is severe muscle wasting—for example, in chronic pyomyositis, active muscle disease may not be associated with an increase above normal, in the level of creatine kinase in blood.

The third striking observation in this study was the finding of elevated CSF tau in 14/76 (18%) patients and the association between elevated CSF tau and poor survival. Of those with diagnoses other than HADC, elevated CSF tau was seen in conditions causing cerebral necrosis—for example, viral encephalitis due to CMV or VZV and cerebral toxoplasmosis. It is tempting to suggest that the five patients with HADC and elevated CSF tau neuropathologically might have had a more encephalitic process. We are unable to confirm this possibility as we do not have necropsy data on this subgroup of 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.

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Contributors: All authors contributed to the design of the study, to data collection and analysis, and to writing drafts of the manuscript. AJEG performed the tau analyses; MAH-C 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, AJEG, and RFM.

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