CSF biomarkers of Alzheimer disease in HIV-associated neurologic disease

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ABSTRACT

Background: HIV-associated neurologic disorders (HAND) continue to develop in many patients with HIV. CSF amyloid measurements in HAND have been reported to be similar to those in dementia of the Alzheimer type (DAT). Confirmatory evaluation of this finding in carefully evaluated subjects is needed.

Methods: CSF specimens were obtained from subjects clinically categorized with normal cognition from the general population, HIV+ subjects with normal cognition, HIV+ subjects with impaired cognition, or presumed HIV− subjects with mild DAT. CSF measurements of β-amyloid$_{(1-42)}$ (Aβ42), β-amyloid$_{(1-40)}$ (Aβ40), total tau (t-tau), and phosphorylated tau (p-tau181) were performed.

Results: CSF Aβ42 measured in 49 HAND subjects had a median level of 501 pg/mL, which was lower than that of 50 controls of similar age who had median of 686 pg/mL ($p < 0.0001$) or 21 HIV+ subjects without cognitive impairment who had median of 716 pg/mL ($p < 0.003$). HAND subjects had similar CSF Aβ42 to 68 subjects with mild DAT. There was no difference of CSF Aβ40 between the groups. Tau and p-tau181 was elevated in DAT, but slightly lower than control in both HIV+ groups.

Conclusions: β-Amyloid$_{(1-42)}$ (Aβ42) measurements in CSF of cognitively impaired patients with HIV are similar to those in patients with mild dementia of the Alzheimer type (DAT). Normal or slightly depressed CSF tau and p-tau181 measurements distinguish these patients with HIV-associated neurologic disorders (HAND) from patients with DAT. Further evaluation of amyloid metabolism in patients with HIV cognitive disorder is needed to understand the implications of depressed CSF Aβ42 in the setting of HAND. *Neurology*® **2009;73:1982–1987**

GLOSSARY

Aβ = β-amyloid; **AD** = Alzheimer disease; **APP** = amyloid precursor protein; **CDR** = Clinical Dementia Rating; **CHARTER** = CNS Highly Activated Retroviral Therapy Effects Research; **DAT** = dementia of the Alzheimer type; **HAD** = HIV-associated dementia; **HAND** = HIV-associated neurologic disorders; **LRP** = lipoprotein receptor related protein; **MCD** = mild cognitive disorder; **NNTC** = National NeuroAIDS Tissue Consortium; **p-tau181** = phosphorylated tau; **t-tau** = total tau.

HIV-associated neurocognitive disorders (HAND) continue to be a problem in HIV-infected (HIV+) subjects despite generally successful virologic control with modern antiretroviral agents. The pathophysiology of observed deficits in HAND is incompletely understood, but appears to be enhanced by aging, consistent with an interaction of aging seen for other neurodegenerative processes.[1] Measurements of CSF β-amyloid$_{(1-42)}$ (Aβ42), total tau (t-tau), and phosphorylated tau (p-tau181) in advanced HAND, Alzheimer disease (AD), and age-matched seronegative controls have been reported previously.[2] HAND subjects had significantly decreased CSF Aβ42 and increased t-tau and p-tau181 concentrations similar to patients with AD, suggesting that HAND may be associated with AD or an AD-like process. Additional observations linking HAND and amyloid-associated processes include reports of neuropatho-

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logic evidence of amyloid deposition in the brains of HIV+ patients,[3] of more silver stained (i.e., neuritic) amyloid plaques in HIV+ patients than in controls of the same age,[4] and a demonstration of increased diffuse plaques in HIV brains.[5] It has been demonstrated that in neural cell membranes from human brain aggregates, the HIV-1 transactivator regulatory protein Tat may inhibit neprolysin, an endonuclease for Aβ breakdown, the primary peptide constituent of amyloid in AD.[5]

Given the expanding insights for therapeutics to address abnormal Aβ metabolism in AD, clear demonstration of the role of similar pathophysiologic properties in HAND could be of substantial importance. Previous reports[2] are provocative, but incomplete since this article did not report Aβ40, which specifically remains normal when Aβ42 declines in AD.[6] Specific reductions in CSF Aβ42 have been shown to be associated with brain amyloid deposition as evidenced by PET imaging of the amyloid-binding agent Pittsburgh Compound B.[7] The interpretation of decreased levels of CSF Aβ42 as being due to possible AD processes would be different in the face of concomitant decreases in Aβ40. Further, the findings of the previous report[2] regarding tau levels in HAND are at variance to several prior studies.[8,9] In the present study, we compared CSF values of Aβ and tau within long-term infected HIV+ subjects with known cognitive status to age-matched HIV uninfected controls and patients diagnosed with mild dementia of the Alzheimer type (DAT).

METHODS

Subjects. CSF from clinically characterized HIV+ patients was obtained from both the National NeuroAIDS Tissue Consortium (NNTC) and from the Washington University in St. Louis cohort of the CNS Highly Activated Retroviral Therapy Effects Research (CHARTER) study. All subjects gave written informed consent under the direction of the local institutional review boards for human studies. For both cohort studies from which data were used, all subjects had neuropsychometric and neurologic examinations leading to classification of cognitive impairment. NNTC subjects were enrolled due to advanced HIV disease with anticipated imminent death. All 41 CSF samples from the NNTC cohort had HAND, either classified as HIV-associated dementia (HAD) (n = 11) or mild cognitive disorder (MCD) (n = 30), both of which require impaired performance on a broad neuropsychometric battery and evidence of functional impairment. Within the CHARTER cohort, an additional 8 subjects had HAND, with the rest (n = 21) having normal performance on concurrent neurologic examination and neuropsychometric testing. Diagnostic classification of HAND is not made in the face of serious comorbid conditions that might be alternative explanations for neurocognitive performance deficits.

Controls were derived from a clinically well-characterized group of adults volunteering for evaluation at the Washington University Memory and Aging Project. Careful examination and testing was performed with participants categorized by the Clinical Dementia Rating (CDR) scale as unimpaired (CDR = 0) or having mild impairment that has a high correlation with histologic AD in subsequent neuropathologic examinations (CDR = 0.5).[6]

CSF handling and evaluation. CSF samples obtained from the NNTC had been rapidly frozen and stored and shipped frozen to Washington University for analysis. The control samples were placed on ice immediately during the lumbar puncture, and stored frozen until time of analysis. HIV samples were also quickly frozen and thawed only once for the analysis. Control and DAT samples were collected at 7:30 AM, while the times of collection for the HIV samples were random daytime hours.

CSF samples were analyzed for total tau, phospho-tau$_{181}$ (p-tau181), and Aβ_{42} by commercial ELISA (Innotest, Innogenetics, Ghent, Belgium), and Aβ_{40} by ELISA as previously described by Fagan et al.[7] For all measures, samples were continuously kept on ice, and assays were performed on sample aliquots after a single thaw following initial freezing.

Statistical analysis. Standard descriptive statistics were calculated for each population in the study. CSF Aβ42 and Aβ40 measurements were log transformed to approximate a normal distribution. CSF tau and p-tau181 required log-log transformation to approximate a normal distribution. Contrasts of biomarker measurements among the control, DAT, HIV, and HAND groups were performed using analysis of covariance after adjusting for age. p Values for pairwise comparisons were taken from the least squares means difference matrix with a significant difference if $p < 0.05$. Correlations among CD4, nadir CD4, plasma viral load, and CSF viral load were calculated using Pearson correlation coefficient. All statistical analyses were performed using SAS version 9.1.

RESULTS

Table 1 provides demographic variables for neurologically normal HIV-positive patients, HAND subjects, DAT subjects, and nondemented controls. Overall, the DAT cohort was older than any other group (for all contrasts $p < 0.0001$). We dealt with this difference in age by including age as a covariate in the analyses. Most patients with HIV, but not all, were taking antiretroviral therapy. Within the HIV+ subgroups, HAND patients had a trend toward lower nadir and current CD4 counts and higher plasma viral loads than cognitively normal HIV+ patients. However, none of the differences is significant. Median CSF viral load was higher in the neurologically normal HIV+ subjects. CSF biomarkers results are presented in table 2 and demonstrated in the figure. CSF Aβ42 in the HAND HIV group was significantly lower than unaffected controls or neurologically normal HIV+

Table 1 Characteristics of each sample

	No.	Age, y, mean (SD)	CD4, cells/mm^3, mean (median)	Nadir CD4, cells/mm^3, mean (median)	Plasma HIV viral load, c/mL, mean (median)	CSF HIV viral load, c/mL, mean (median)
Control	50	50 (3.02)	NA	NA	NA	NA
DAT	68	74 (7.39)	NA	NA	NA	NA
Neuro normal HIV+	21	43 (9.18)	421 (389)	218 (225)	19,317 (13,000)	5,750 (671)
HAND HIV+	49	48 (8.03)	348 (320)	176 (117)	127,067 (452)	4,450 (<50)

Control without dementia (Control), mild (Clinical Dementia Rating 0.5/1.0) dementia of the Alzheimer type (DAT), neurocognitively normal HIV-positive (HIV), and neurocognitively impaired HIV-associated neurologic disorder (HAND) samples are shown.

subjects. Even after statistical corrections for the differences in age between DAT and HAND subjects, the CSF Aβ42 levels in HAND subjects are not significantly different from CSF Aβ42 levels in DAT subjects ($p = 0.25$). CSF Aβ40 levels were similar for all groups. In contrast, CSF tau and p-tau181 (the primary constituents of neurofibrillary tangles in AD) for both neurologically normal and HAND HIV+ groups were slightly lower than unaffected controls, and did not mirror the significant elevations typically seen with DAT (figure).

We also sought to identify possible associations of the biomarker findings with important measures of the biology of HIV disease including current CD4 count, nadir CD4 count, current plasma viral load, and current CSF viral load. Pearson correlation coefficients were derived and revealed no significant correlations of any single HIV disease markers to any of the 4 AD biomarkers we studied (table 3).

DISCUSSION In clinically well-characterized subjects, we find that HIV-positive subjects with neurocognitive impairment have significantly lower CSF Aβ42 than unimpaired subjects, comparable to findings in mild DAT. However, we find that the tau elevations characteristic of DAT are absent in HAND. Our findings suggest that there is a change in Aβ42 metabolism occurring with the development of HIV-associated neurologic dysfunction. Age-related changes in Aβ42 do not account for differences since the HAND and control populations had similar ages, and all analyses include age as a covariate. The observed reduction in CSF Aβ42 in cognitively impaired HIV-positive patients is consistent with an earlier report[2] and, in the absence of reductions in CSF Aβ40, suggests that the reductions in Aβ42 may be indicative of brain amyloid deposition and not just death of neurons. However, in contrast to an earlier report,[2] and consistent with other studies,[8,9] we observed that CSF tau and p-tau181 were not elevated in association with reductions in CSF Aβ42. This CSF profile helps distinguish HIV from DAT, implicating abnormalities in amyloid metabolism in HAND, with no evidence of the tauopathy that occurs in DAT. Another recent report[10] shows similar findings with regard to Aβ42, associating lower CSF Aβ42 but normal p-tau181 with symptomatic HIV-associated cognitive disease. However, this report continues to suggest total tau was elevated in CSF of this population. The reason for the disparity in tau measurements is unclear, although one possible difference is that these patients were untreated for HIV, whereas our symptomatic patients were generally taking antiretroviral therapy. It is possible that participants in this study may have had more active or ongoing neuropathology due to lack of HIV treatment. However, this report of normal tau in the DAT patients is also discordant with AD literature. Together, our findings suggest that measurements of certain tau species in CSF may be useful as a means of differentiating HIV-associated cognitive decline from AD. Because of the aging of the HIV-positive population, this distinction may well be of increasing utility.

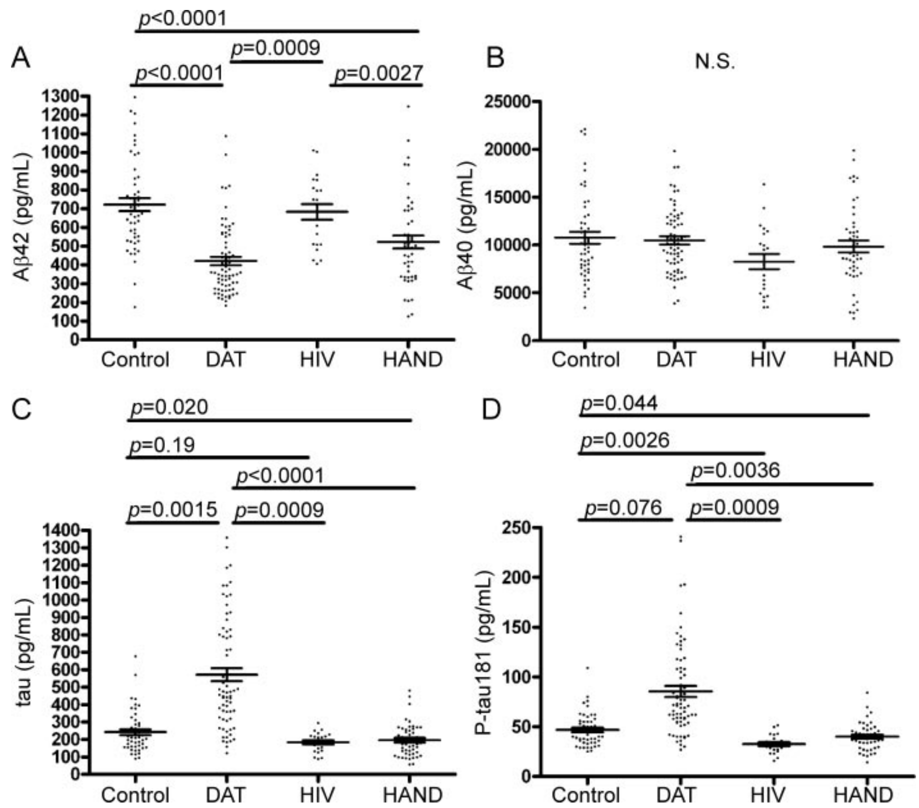
Further consideration of the reasons for low CSF Aβ42 in HAND require ongoing research. Reductions in CSF Aβ42 levels have been shown to be a reliable marker for brain amyloid deposition in patients with AD as well as a subset of cognitively normal elderly individuals hypothesized to have "preclinical" AD (i.e., amyloid deposition prior to

Table 2 Mean (median) values of biomarkers in each sample

	CSF biomarkers			
	Aβ42, pg/mL	Aβ40, pg/mL	Tau, pg/mL	p-tau 181, pg/mL
Control	722 (686)	10,773 (9,875)	242 (212)	47 (44)
DAT	421 (359)	10,492 (10,128)	572 (475)	85 (71)
Neuro normal HIV	683 (716)	8,267 (7,921)	183 (191)	33 (32)
HAND HIV	522 (501)	9,852 (9,051)	196 (174)	40 (39)

Aβ42, Aβ40, tau, and p-tau mean and median values for controls without dementia (Control), mild (Clinical Dementia Rating 0.5/1.0) dementia of the Alzheimer type (DAT), neurocognitively normal HIV-positive (HIV), and neurocognitively impaired HIV-associated neurological disorder (HAND). See figure for significance of contrasts.

Figure CSF biomarkers



(A) Aβ42 levels in HIV-negative controls without dementia (controls), individuals with dementia of the Alzheimer type (DAT), HIV-positive individuals without dementia (HIV), and individuals with HIV-associated neurologic disorders (HAND). *p* Values of less than 0.05 from the least squares means difference matrix are shown. (B) Aβ40 levels in the 4 groups. There are no significant differences. (C) Tau levels in the 4 groups. DAT is significantly higher than all other groups. Both HIV and HAND are significantly lower than controls. No other significant associations. (D) p-tau181 levels in the 4 groups. DAT is significantly higher than controls, HIV, and HAND. The HAND group is significantly lower than controls. No other significant associations.

the onset of clinical dementia symptoms).[11-14] While the pathology of HAND and AD differs significantly,[15] it will be important to see if PET amyloid imaging in vivo can distinguish these forms of dementia despite the similarity of the CSF Aβ42 levels. We assume that in HIV, if amyloid deposition is occurring, there will be a much greater percentage of diffuse, nonfibrillar Aβ deposits as compared to what is typically seen in AD, given the absence of florid amyloid plaques in HIV neuropathology.

There are reasons that could explain altered Aβ metabolism in HIV disease. HIV Tat protein has been shown to inhibit an Aβ cleaving protein, neprilysin, which could lead to increased brain amyloid deposition.[5] Alternatively, HIV Tat may compete with the amyloid precursor protein (APP) and apolipoprotein E (an Aβ chaperone) for binding to the low density lipoprotein receptor related protein (LRP), thus blocking LRP-mediated clearance of Aβ from brain interstitial fluid to peripheral compartments.[16] On the other hand, soluble APP cleavage products (sAPPα and sAPPβ) have been reported to be reduced in the CSF of patients with HAND compared to those with DAT or HIV-negative controls, with sAPPα showing a slight decline in the asymptomatic HIV state.[17] These findings, in conjunction with the low Aβ42 in HIV, might suggest that synthesis of the amyloid precursor (APP) declines with symptomatic disease. If APP synthesis were decreased, one would expect a decrease in CSF Aβ40 and Aβ42, not just a selective decrease in Aβ42. However, this idea could be tested since Aβ turnover is quite a dynamic process, approximating 8% turnover per hour,[18] and could be assessed directly.

Our findings reinforce the importance of understanding the significant change in amyloid metabolism that is associated with symptomatic HIV-associated neurologic disease and may expand considerations of the pathophysiology of HAND. The failure of HIV viral load and CD4 counts to correlate with development of HAND in our HIV-positive patients reinforces the need for reliable predictive biomarkers for this widespread problem. While CSF viral load was previously re-

Table 3 **Pearson correlation coefficients comparing CD4, nadir CD4, plasma HIV viral load, and CSF HIV viral load with the 4 CSF biomarkers**

	CD4	Nadir CD4	Plasma viral load	CSF viral load
Aβ42	0.04967	−0.01721	−0.04829	0.03366
p Value	0.6875	0.8909	0.698	0.7789
No.	68	66	67	72
Aβ40	−0.20002	−0.0902	0.04676	0.19117
p Value	0.1046	0.4749	0.7093	0.1184
No.	67	65	66	68
Tau	−0.17622	−0.20969	−0.02007	−0.00995
p Value	0.1506	0.0911	0.8719	0.9339
No.	68	66	67	72
p-tau181	−0.18255	−0.16487	0.00508	0.00172
p Value	0.1362	0.1859	0.9675	0.9885
No.	68	66	67	72

There are no significant correlations.

lated to development of dementia, in the current treatment era this is no longer the case, as we found in this analysis.[19,20]

Successful HIV therapy is resulting in long survival of patients with HIV, who are now entering age brackets where AD becomes more common. In aging patients developing dementia, our findings suggest that CSF tau measurements are likely to distinguish patients with HAND from those with AD. While age was included as a covariate in our analyses to account for age-related changes, it may be necessary to confirm that CSF tau distinguishes HAND from DAT once a substantial sample of older patients with HAND comparable in age to DAT samples are available for analysis. Meanwhile, emerging technologies such as assessment of amyloid deposition in the brain with PET imaging and defining the dynamics of Aβ production and elimination may clarify the basis for the changes being observed.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. John S.K. Kauwe.

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DISCLOSURE

The study was funded by NIH grant MH22005. Dr. Clifford serves/has served on scientific advisory boards for Biogen Idec, Elan Corporation, Roche, Forest Laboratories, Inc., Genentech, Inc., GlaxoSmithKline, Millennium Pharmaceuticals, Inc., Schering-Plough Corp., Bristol-Meyers Squibb, and Genzyme Corporation; received speaker honorarium and funding for travel from GlaxoSmithKline; has received research support from Pfizer Inc., Schering-Plough Corp., Bavarian Nordic, NeurogesX, GlaxoSmithKline, Tibotec Therapeutics, Boehringer Ingelheim, and Gilead Sciences, Inc.; and receives research support from the NIH [UO1 NS32228 (PI) , UO1 AI69495 (PI), NIMH 22005 CHARTER Project (Site PI), NIDA RO3 DA022137 (Co-I), NIMH MH058076 (Site PI), and R21 3857-53187 (PI)]. Dr. Fagan serves on a speakers' bureau for the Alzheimer's Association. Dr. Holtzman serves on scientific advisory boards for Satori Pharmaceuticals and EnVivo Pharmaceuticals; serves as an Associate Editor of *Annals of Neurology*, the *Journal of Neuroscience*, *Neurobiology of Disease*, and *Experimental Neurology*; may accrue revenue on pending US Patent 20080145941 (filed 6/18/08): Methods for Measuring the Metabolism of Neurally Derived Biomolecules in Vivo, pending US Patent 20090074775 (filed 3/19/09): Use of Anti-AB Antibody to Treat Traumatic Brain Injury, pending US Patent 20090035298 (filed 2/5/09): Methods to Treat Alzheimer's Disease or Other Amyloid Beta Accumulation Associated disorders; US Patent 7,195,761 (issued 3/27/07): Humanized antibodies that sequester abeta peptide, US Patent 7,015,044 (issued 3/21/06): Diagnostic for early stage Alzheimer's disease, US Patent 6,465,195 (issued 10/15/02): Predictive diagnostic for Alzheimer's disease; serves as a consultant to Merck Serono, Eli Lilly and Company, Takeda Pharmaceutical Company Limited, Abbott, Comentis, Inc., Eisai Inc., and AstraZeneca; is cofounder of and receives board of directors compensation from C2N Diagnostics LLC; receives research support from AstraZeneca, Pfizer Inc., Eli Lilly and Company, Elan Corporation, Forest Laboratories, Inc., the NIH [NIA R37 AG13956 (PI), NINDS 1P30NS057105 (PI), NINDS P01-NS35902 (PI of project 3), NINDS P01-NS32636 (PI of project 3), NIA P01-AG026276 (Co-I), NIA R01-AG025824 (I), NINDS R01-NS034467 (I), NIA U01AG032438 (Co-I), NIA PO1-AG03991(PI of project 2)], Cure Alzheimer's Fund, and Fidelity Foundation; has received compensation from Washington University from license revenue received for licensing of patent application entitled "Methods for Measuring the Metabolism of Neurally Derived Biomolecules in Vivo" to C2N Diagnostics LLC; and may receive future royalty payments for Washington University licensing patent entitled "Methods for Measuring the Metabolism of Neurally Derived Biomolecules in Vivo" to C2N Diagnostics, LLC, and could receive future royalty payments from Washington University for licensing patent entitled "Humanized antibodies that sequester abeta peptide" US Patent 7,195,761 to Eli Lilly and Company. Dr. Morris serves on scientific advisory boards for AstraZeneca, Bristol-Myers Squibb, Genentech, Inc., Merck Serono, Novartis, Pfizer Inc., Schering-Plough Corp., Eli Lilly and Company, Wyeth, and Elan Corporation; serves on the editorial advisory board of *Alzheimer's Disease and Associated Disorders*; receives royalties from publishing *Mild Cognitive Impairment and Early Alzheimer's Disease* (John Wiley and Sons, 2008), *Dementia* (Clinical Publishing, 2007), *Handbook of Dementing Illnesses, 2 Ed* (Taylor & Francis, 2006), and for an editorial in *Lancet Neurology* (Elsevier, 2008); and receives research support from Elan Corporation, Wyeth, Eli Lilly and Company, Novartis, Pfizer Inc., Avid Radiopharmaceuticals, the NIH/NIA [P50AG05681 (PI), P01AG03991 (PI), P01AG026276 (PI), U01AG032438 (PI), U01AG024904 (Neuropathology Core Leader), R01AG16335 (Consultant), and P50NS006833 (Investigator), and from the Dana Foundation. A.R. Shah, Dr. Teshome, and Dr. Kauwe report no disclosures.

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