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CSF Markers of AD-Related Pathology Relate Specifically to Memory Impairment in Older People with HIV: A Pilot Study

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Abstract

Given the co-occurrence of memory impairment in HIV-associated neurocognitive disorders (HAND) and amnestic mild cognitive impairment/Alzheimer's disease (aMCI/AD), biomarkers are needed that can disentangle these conditions among people with HIV (PWH). We assessed whether cerebrospinal fluid (CSF) markers of AD could help in this effort by determining their relationship to learning and memory deficits versus cognitive deficits more characteristic of HAND than aMCI/AD (processing speed and complex visual/motor coordination) among 31 older PWH. CSF amyloid-β_{42}, phosphorylated-Tau, amyloid-β_{40}/amyloid-β_{42} and phosphorylated-Tau/amyloid-β_{42} ratio related to learning/memory performance but not HAND-related deficits, suggesting that these biomarkers may have utility in disentangling aMCI/AD from HAND.

Keywords

mild cognitive impairment; Alzheimer's disease; HIV-associated neurocognitive disorders; biomarkers; Tau; amyloid

Background

Advances in antiretroviral therapy (ART) have led to increased longevity in people with HIV (PWH), yet HIV-associated neurocognitive disorders (HAND) persist in 45% of PWH[1]. Additionally, more than half of PWH who are over age 50 in the U.S.[2–5] will be at risk for age-related neurodegenerative disorders including Alzheimer's disease (AD) and its precursor, amnestic mild cognitive impairment (aMCI). Clinicians are presented with the new challenge of disentangling aMCI/AD versus HAND given overlap in their neurocognitive profiles. Although the cognitive domains impacted by HAND are variable, episodic memory deficits (a defining feature of aMCI/AD[6]) commonly characterize HAND

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in the ART era[7]. Due to their overlapping clinical profile, there is a pressing need to identify biomarkers that can help clinicians distinguish older PWH who may be on the aMCI/AD trajectory from those with HAND in order to intervene appropriately.

The need for methods to identify aMCI in older PWH may be particularly important given that PWH may experience more AD risk factors compared to the general population. HIV-related biological mechanisms and ART medications are associated with chronic inflammation, hyperlipidemia, insulin resistance, and excitotoxic effects of HIV viral proteins, which are all conditions that impart risks for aMCI/AD[8–10]. Age-associated conditions also tend to appear 5-10 years earlier among PWH than in the general population[11,12], suggesting a "premature aging" phenomenon among PWH. Because of the more neurodegenerative profile of aMCI/AD versus HAND, the risk of delayed aMCI/AD diagnosis among older PWH is a pressing issue in geriatric neuroHIV[13]. Given the overlapping clinical profiles of aMCI and HAND, biomarkers may be particularly beneficial in these strategies.

Amyloid-β ($A\beta_{42}$) plaque deposits and neurofibrillary tangles of phosphorylated-tau (p-tau_{181}.) protein are hallmark pathological characteristics of AD and often develop prior to cognitive deficits[14]. In contrast, HAND is more neuropathologically heterogeneous and ubiquitous defining characteristic have not been identified[15]. $A\beta_{42}$ plaque deposits have been observed in the brains of post-mortem HIV cases although plaque burden is typically lower in PWH than in AD patients[1,10,16–19]. Evidence of p-tau_{181} pathology in HIV has been less consistent, with studies reporting that brain or cerebrospinal fluid (CSF) levels of p-tau were similar[6,20,21], higher[22,23], or slightly lower [24] in PWH in comparison to age-matched HIV-seronegative controls. It is unclear whether the evidence of $A\beta_{42}$ and p-tau_{181} in HAND cases reflects early AD-associated pathogenesis or a commonality in pathological mechanisms of AD and HAND. Thus, the utility of in-life CSF levels of $A\beta_{42}$ and p-tau_{181} in disentangling aMCI from HAND among PWH is unknown. The current study was aimed to determine if CSF markers of AD pathology can aid in disentangling AD- versus HAND-related cognitive deficits among older PWH. To do so, we examined how these CSF markers relate to memory deficits versus other cognitive deficits (processing speed and complex visual/motor coordination) that characterize HAND more so than early-stage AD. We hypothesized that the CSF AD markers would show a stronger relationship with memory versus the HAND-related domains.

Methods

Participants

The current study examined PWH from the National NeuroAIDs Tissue Consortium (NNTC, www.nntc.org)[25]. Exclusion criteria for the overall NNTC are minimal. In the present study, we included those who were age ≥50 years and had available data on CSF $A\beta_{42}$ and p-tau_{181} levels, neurocognitive function and covariates (e.g., apolipoprotein-E ε4 allele [ApoE4]). Human Research Protections Program at each NNTC site approved study procedures and participants provided written informed consent. The final sample consisted of 31 PWH participants aged 50-68 years old. Participants completed comprehensive neuromedical, neurocognitive and neurobehavioral assessments during study visits.

CSF AD Biomarkers

CSF levels of p-Tau_{181} (Fujirebio, Belgium) and $A\beta_{42}$ (Meso Scale Discovery, Rockville, MD) were measured by using commercial suspension array immunoassay. Due to a non-normal distribution as determined by the Shapiro-Wilks test, we used log_{10} transformed p-tau_{181} concentrations in analyses to improve normality. Our CSF AD biomarkers included levels of $A\beta_{42}$, log_{10}-transformed p-tau_{181}, the ratio of p-tau_{181} to $A\beta_{42}$ (p-tau_{181}/$A\beta_{42}$) and the ratio of $A\beta_{40}$ to $A\beta_{42}$ ($A\beta_{40}$/$A\beta_{42}$). Greater pathological burden is reflected by lower levels of $A\beta_{42}$ and higher levels of p-tau_{181} , the p-tau_{181}/$A\beta_{42}$ ratio[26] and $A\beta_{40}$/$A\beta_{42}$ ratio.

Neuromedical Evaluation

HIV disease characteristics were determined via self-reports and/or laboratory tests. Estimated duration of HIV disease was self-reported. Nadir CD4+ T-cell count was the lowest lifetime value among self-report and study obtained CD4+ T-cell counts and released medical records. CD4+ T-cell count was measured with flow cytometry and antemortem plasma HIV-1 RNA level was measured by ultra-sensitive PCR (Amplicor, Roche Diagnostic System, Indianapolis, IN; lower limit of detection <50 copies/ml) in a CLIA-certified clinical laboratory. Hepatitis C serostatus was determined by enzyme-linked immunosorbent assay. History of substance use disorders was assessed via the Composite International Diagnostic Interview[27], a computer-based structured interview, and diagnoses were based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). Genotyping of the apolipoprotein-E ε4 (APOE4) allele, the strongest genetic risk factor for sporadic AD, was conducted via the allelic discrimination assay (Taqman® SNP Genotyping Assays, Applied Biosystems).

Neurocognitive Evaluation

Participants completed a standardized neurocognitive test battery of verbal fluency, working memory, speed of information processing, verbal and visual learning and delayed recall, executive function, and complex motor function. We chose to specifically examine domains in which impairment defines aMCI (episodic memory) or is more characteristic of HAND versus early-stage AD (speed of information processing, fine motor control) in order to limit the number of comparisons in this small sample to hypothesis-driven comparisons that can address the aMCI versus HAND disentangling utility of the biomarkers. Our neurocognitive outcomes included tests of episodic memory, as well as tests measuring speed of information processing and complex visual/motor coordination, as these domains are commonly impaired in HAND in the ART era[28]. Our episodic memory measures were the Learning and Delayed Recall raw scores from the Hopkins Verbal Learning Test – Revised (HVLT-R)[29] and the Brief Visuospatial Memory Test – Revised (BVMT-R)[30]. Our measure of speed of information processing was the Wechsler Adult Intelligence Scale-III (WAIS-III) Digit Symbol Test and Symbol Search Test as well as the Trail Making Test (TMT) – part A score[31]. TMT scores were transformed in order to improve distribution and so that, in line with other tests, higher scores reflect better performance. Complex visual/motor coordination was assessed with the combined raw score of the dominant and non-dominant hand trials of the Grooved Pegboard Test. Details of the specific tests are described elsewhere[32].

A series of multiple linear regressions were conducted to examine the association between individual CSF biomarker levels ($A\beta_{42}$, p-Tau_{181}, and p-Tau/$A\beta_{42}$ ratio) and each cognitive outcome (BVMT-R and HVLT-R Learning and Delayed Recall, Digit Symbol, Symbol Search, TMT- part A and Grooved Pegboard), while controlling for covariates. Considered covariates included age, sex, race, education, estimated duration of HIV in years, current and nadir CD4+ T-cell counts, APOE4 carrier status, hepatitis C serostatus, ART status, and current or lifetime substance use disorder diagnosis. Covariates were included in the initial regression models and, if significant at p=<.10, they were retained in the final model.

Results

The sample was 84.9% male, 58.1% Caucasian with a mean age of 56.3 years (SD=5.8). Table 1 displays sample characteristics including mean AD biomarker levels[33,34,35].

$A\beta_{42}$ concentration

In linear regressions modeling $A\beta_{42}$ levels in relation to cognitive performance, significant covariates included in the model were age (BVMT-R Delayed Recall and Grooved Pegboard models), current substance use disorder (HVLT-R Learning and Delay Recall models), race (HVLT-R Delayed Recall, Digit Symbol Search and TMT-part A model), HIV duration, ApoE4 genotype, hepatitis C virus seropositivity, past substance use disorder (HVLT-R Delayed Recall model), and nadir CD4+ T-cell count (WAIS-III Digit Summary, Digit Symbol Search, TMT-Part A and Grooved Pegboard model). Higher $A\beta_{42}$ levels were associated with better BVMT-R Learning performance (Figure 1A). Conversely, $A\beta_{42}$ levels were not associated with BVMT-R Delayed Recall, HVLT-R Learning or Delayed Recall, Digit Symbol, Symbol Search, TMT-Part A or Grooved Pegboard scores.

p-Tau_{181} concentration

In linear regressions modeling p-tau_{181} levels in relation to cognitive performance, significant covariates included in the model were age (BVMT-R Delayed Recall and Grooved Pegboard models), current substance use disorder (HVLT-R Learning and Delayed Recall models), race (HVLT-R Delayed Recall and Symbol Search model), HIV duration, ApoE4 genotype, past substance use disorder (HVLT-R Delayed Recall model), and nadir CD4+ T-cell count (Digit Symbol, Symbol Search and Grooved Pegboard models). p-tau_{181} levels were not significantly associated with any cognitive outcome.

p-tau_{181}/$A\beta_{42}$ ratio

In linear regressions modeling the p-tau_{181}/$A\beta_{42}$ ratio in relation to cognitive performance, significant covariates included in the model were age (BVMT-R Delayed Recall, HVLT-R Learning and Grooved Pegboard models), current and past substance use disorder (HVLT-R Learning and Delayed Recall models), HIV duration, ApoE4 genotype, and hepatitis C virus seropositivity (HVLT-R Delayed Recall and TMT-Part A model), race (Symbol Search and TMT-Part A model) and nadir CD4+ T-cell count (Digit Symbol, TMT-Part A and Grooved Pegboard models). Higher p-tau_{181}/$A\beta_{42}$ ratio levels were associated with poorer scores on BVMT-R Learning (Figure 1B) and Delayed Recall (Figure 1C) and HVLT-R Delayed

Recall (Figure 1D). p-tau$_{181}$/Aβ$_{42}$ ratio levels were not associated with HVLT-R Learning, Digit Symbol, Symbol Search, TMT-part A or Grooved Pegboard scores.

Aβ$_{40}$/Aβ$_{42}$ ratio

In linear regressions modeling the Aβ$_{40}$/Aβ$_{42}$ ratio in relation to cognitive performance, gender was added as a significant covariate included in the Grooved Pegboard model. Aβ$_{40}$/Aβ$_{42}$ ratio levels were not associated with HVLT-R Learning, HVLT-R Delayed Recall, BVMT-R Learning, BVMT-R Delayed Recall, Digit Symbol, Symbol Search, TMT-part A or Grooved Pegboard scores.

Discussion

This study was motivated by the new challenge faced by clinicians to determine whether memory impairment in older PWH is HAND-related or an evolving dementia due to AD. We aimed to examine the utility of standard CSF AD biomarkers in distinguishing aMCI/AD from HAND by determining how these biomarkers relate to memory versus cognitive domains that are more characteristic of HAND than aMCI/AD among older PWH. This is an important question to address because it is unclear whether prior evidence of Aβ$_{42}$ and p-Tau$_{181}$ pathology among a proportion of older PWH with HAND[17–23] may be indicative of early-stage aMCI/AD or suggests a shared pathological mechanism of aMCI/AD and HAND. In partial support of hypotheses, we found that lower CSF Aβ$_{42}$ levels (greater pathology) related to poorer BVMT-R Learning and higher p-Tau$_{181}$/Aβ$_{42}$ ratio levels (greater pathology) related to poorer BVMT-R Learning & Delayed Recall and HVLT-R Delayed Recall; however, none of the biomarkers related to complex visual/motor or processing speed performance. Our results suggest that these CSF biomarkers are more reflective of early AD-related clinical deficits than HAND and, in conjunction with neuropsychological testing, may help identify older PWH who may be at risk for AD.

Our group previously examined how CSF Aβ$_{42}$ levels and family history of dementia related to HAND among PWH although in a somewhat younger sample (M=43, SD=8)[36]. We found that lower CSF Aβ$_{42}$ levels were associated with HAND only among those with family history of dementia. These findings suggest that CSF Aβ$_{42}$ levels only relate to cognitive deficits in PWH in the context of higher AD genetic risk at-least in this middle-aged sample. Although this previous study did not attempt to identify aMCI-related cognitive deficits amid HAND, the findings support the current results in suggesting that CSF Aβ$_{42}$ levels are an aMCI-specific marker. Interestingly, among our CSF biomarkers, it was the p-tau$_{181}$/Aβ$_{42}$ ratio that more consistently related to memory performance. The broader literature supports our findings such that rates of cognitive decline are greater for older adults with evidence of both amyloid and tau pathology versus just one of these pathologies[37–39]. In a previous report, cognitively normal individuals with a high p-tau$_{181}$/Aβ$_{42}$ ratio, and not just evidence of Aβ$_{42}$ alone, were more likely to show cognitive decline[26]. These findings suggest that the p-Tau$_{181}$/Aβ$_{42}$ ratio may be particularly helpful in distinguishing PWH on an AD trajectory versus those with HAND.

Our study has limitations and implications for future directions. The cross-sectional analyses precluded us from examining the temporal pattern of results. Longitudinal studies are

needed to test whether CSF AD pathology markers are an early marker for incipient cognitive decline and AD among PWH. This pilot study was also limited by the small sample size and the high proportion of men (85%) limited generalizability. Analyses in larger samples with more women are needed to test the replicability and generalizability of our findings to other PWH cohorts. Because of our small sample size, we did not use a statistical correction for our multiple comparisons. However, we feel it is not necessary since we had specific hypotheses about the type and direction of associations with results supporting those hypotheses. Other limitations include a lack of control group and no independent evaluation of amyloid burden using Positron Emission Tomography (PET). Findings from this study provide initial insights into the utility of CSF AD biomarkers in disentangling an aMCI-related cognitive profile from HAND. Future studies are need to build on our initial findings by examining these biomarkers in larger samples and broadening the biomarker panel to other AD-related and HAND-specific biomarkers to aid in diagnosis among PWH.

Overall, these data suggest that CSF markers of AD pathology, particularly the p-tau$_{181}$/Aβ_{42} ratio, relate more so to AD- than HAND-related cognitive deficits among older PWH and thus may help in distinguishing aMCI- from HAND-associated impairment. Identifying AD in its early stages is critical among PWH for both clinical and experimental reasons. Clinically, the more neurodegenerative profile of aMCI/AD requires different life planning and treatment options, compared to the more stable HAND profile. A delayed aMCI/AD diagnosis in PWH would limit the opportunity to intervene early in the course of AD when interventions are most effective and life planning can be better implemented. Experimentally, the identification of aMCI/AD among PLWH will improve studies examining the prevalence and biomarkers, imaging and genetic correlates of HAND among older PWH.

Conflicts of Interest and Source of Funding:

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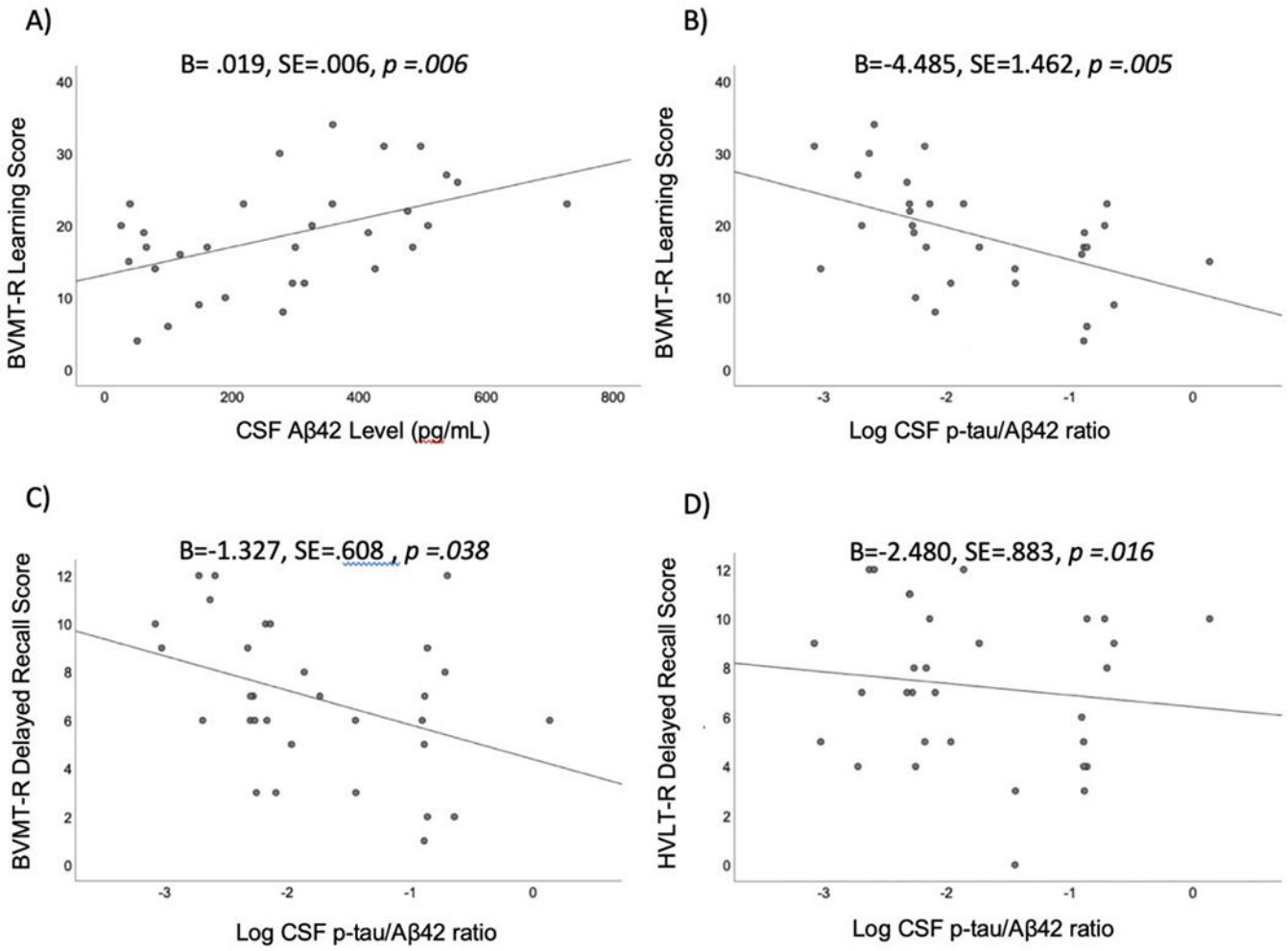

Fig 1.

Scatterplots of significant associations between CSF AD biomarkers and cognitive outcomes: A) $A\beta_{42}$ and BVMT-R Learning, B) p-tau_{181}/$A\beta_{42}$ ratio and BVMT-R Learning, C) p-tau_{181}/$A\beta_{42}$ ratio and BVMT-R Delayed Recall, D) p-tau_{181}/$A\beta_{42}$ ratio and HVLT-R Delayed Recall Score

Table 1

Sample characteristics

Demographics	
Age (years), mean (SD)	56.3 (5.8)
Education (years), mean (SD)	13.0 (2.3)
Race	
White, n (%)	18 (58.1%)
Black, n (%)	12 (38.7%)
Other, n (%)	1 (3.2%)
Ethnicity	
Hispanic, n (%)	2 (6.4%)
Male sex, n (%)	26 (84.9%)
APOE4 carrier, n (%)	6 (19%)
HIV Disease Characteristics	
Nadir CD4+ T-cell count (cells/ul), mean (SD)	85.7 (134.5)
Current CD4+ T-cell count (cells/ul), mean (SD)	221.0 (226.7)
Plasma HIV-1 RNA load, n (% undetectable)	10 (32.3%)
Estimated duration of HIV (years), mean (SD)	14.1 (6.9)
Proportion on ART, n (%)	28 (90.3%)
HAND diagnosis, n (%)	14 (45%)
Hepatitis C seropositive, n (%)	10 (32%)
CSF AD Biomarkers	
$A\beta_{42}$ (pg/mL), mean (SD)	286.6 (189.0)
p-Tau level (pg/mL), mean (SD)	40.3 (20.02)
p-Tau/$A\beta_{42}$ ratio, mean (SD)	−1.8 (0.8)
$A\beta$ $ratio_{40}/A\beta_{42}$ ratio, mean (SD)	0.1(0.2)
Positive $A\beta_{42}$ (<192 pg/mL)[35]* (%)	38.7%
Positive p-Tau level (> 23pg/mL)[33]* (%)	71.9%
Positive p-Tau/$A\beta$ ratio (0.11+)[34]* (%)	64.5%

HAND = HIV Associated Neurocognitive Disorders, ART= Antiretroviral therapy, APOE4= apolipoprotein-E ε4 allele, CSF = cerebrospinal fluid, $A\beta_{42}$ = amyloid-beta, p-Tau = phosphorylated tau.

*We used previously-established cutpoints for positivity from the literature.