Journal of Neuroimmunology 319 (2018) 13–18

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

HIV, prospective memory, and cerebrospinal fluid concentrations of quinolinic acid and phosphorylated Tau

Albert M. Anderson[a,*], David Croteau[b], Ronald J. Ellis[b], Debra Rosario[c,h], Michael Potter[c,h], Gilles J. Guillemin[d,e], Bruce J. Brew[e,f], Steven Paul Woods[g], Scott L. Letendre[c,h]

[a] Department of Medicine, Division of Infectious Diseases, Emory University School of Medicine, Atlanta, GA, United States
[b] Department of Neurosciences, University of California at San Diego, La Jolla, CA, United States
[c] Department of Medicine, University of California at San Diego, La Jolla, CA, United States
[d] Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Australia
[e] Peter Duncan Neurosciences Research Unit, St Vincent's Centre for Applied Medical Research, Sydney, Australia
[f] Department of Neurology, St Vincent's Hospital, Sydney, Australia
[g] Department of Psychology, University of Houston, Houston, TX, United States
[h] Department of Psychiatry, University of California at San Diego, La Jolla, CA, United States

ARTICLE INFO

Keywords:
Human immunodeficiency virus
Acquired immunodeficiency syndrome
Neurocognitive disorder
Cerebrospinal fluid
Tau proteins
Tryptophan

ABSTRACT

There is mounting evidence that prospective memory (PM) is impaired during HIV infection despite treatment. In this prospective study, 66 adults (43 HIV+ and 23 HIV negative) underwent PM assessment and cerebrospinal fluid (CSF) examination. HIV+ participants had significantly lower PM but significantly higher CSF concentrations of CXCL10 and quinolinic acid (QUIN). Higher CSF phosphorylated Tau (pTau) was associated with worse PM. In a secondary analysis excluding outliers, higher QUIN correlated with higher pTau. CSF QUIN is thus elevated during HIV infection despite antiretroviral therapy and could indirectly contribute to impaired PM by influencing the formation of pTau.

1. Introduction

HIV-associated neurocognitive disorders (HAND) are persistently common in the combination antiretroviral (cART) era. Up to 40% of HIV+ adults with undetectable plasma HIV RNA levels and minimal neuropsychological comorbidities have at least mild neurocognitive impairment (Heaton et al., 2010). Biological evidence of ongoing neuronal damage during cART comes from magnetic resonance spectroscopy studies as well as studies of neuronal injury biomarkers such as neurofilament-light (Harezlak et al., 2011; Jessen Krut et al., 2014). Yet, the underlying pathogenesis of neuronal damage during cART remains poorly understood.

While inflammation persists during treated HIV and may be a cause of neuronal damage (Zayyad and Spudich, 2015), other processes could also contribute to HAND pathogenesis. Quinolinic acid (QUIN), for example, is a neurotoxin that is a product of the kynurenine pathway for tryptophan metabolism (Vecsei et al., 2013). CSF QUIN levels are elevated during HIV-associated dementia in the absence of cART (Heyes et al., 1991). The ratio of kynurenine to tryptophan (known at the K/T ratio) reflects increased activity of the kynurenine pathway and is associated with mortality when measured from the blood of HIV-infected individuals (Byakwaga et al., 2014). Similarly, the CSF QUIN/T ratio was found to be the earliest predictor of neurological disease in untreated simian immunodeficiency virus (SIV)-infected macaques, and kynurenine pathway metabolites in the brain do not normalize in the SIV-infected brain despite cART (Drewes et al., 2015).

There are also lingering questions as to whether HAND has any pathogenic similarities with Alzheimer's disease (AD), the most common dementia worldwide. The tau protein, which is critical for the stabilization of microtubules and neuronal integrity, is hyperphosphorylated in AD and other dementias (Brunden et al., 2009). Several studies have attempted to determine whether HIV is also associated with abnormal Tau levels and might represent a "Tauopathy". Studies in the pre-cART era focusing on total Tau (t-Tau) were small, and the results were conflicting (Andersson et al., 1999; Green et al., 2000). More recent studies have focused on phosphorylated Tau (pTau), which is more specific for Tauopathy-associated dementias. Again, some studies found a relationship between increased CSF pTau and HAND (Brew et al., 2005), while others did not (Clifford et al., 2009; Krut et al., 2016; Peterson et al., 2014).

A study published in 2006 from the HIV Neurobehavioral Research Program (HNRP) at the University of California at San Diego focused on

* Corresponding author at: Emory University School of Medicine, 341 Ponce de Leon Avenue, Atlanta, GA 30308, United States.
E-mail address: aande2@emory.edu (A.M. Anderson).

https://doi.org/10.1016/j.jneuroim.2018.03.007
Received 28 November 2017; Received in revised form 13 March 2018; Accepted 13 March 2018

the relationship between t-Tau and the specific cognitive domain of prospective memory (PM) (Woods et al., 2006). PM relates to the execution of a future intention, also known as "remembering to remember". Diminished PM is common among persons with HIV disease and is strongly associated with dependence in a wide range of activities of daily living in both older adults and in HIV-infected individuals (Woods et al., 2008a, 2012). The earlier HNRP study demonstrated that CSF t-Tau levels correlated inversely with PM. In the current study, we examined the relationship between PM and the more specific pTau in a new cohort of HIV-infected individuals. QUIN has been shown to induce the phosphorylation of Tau in vitro and co-localizes with hyperphosphorylated Tau in cortical neurons of the brain during AD (Rahman et al., 2009). Therefore, we also measured CSF kynurenine metabolites including QUIN, as well as other selected markers that have been associated with HIV and HAND.

2. Methods

2.1. Assessment of participants

A cohort of HIV-infected (HIV+) and HIV-uninfected (HIVnegative) adults was prospectively recruited at the HNRP. Exclusion criteria were: 1) Positive urine drug screen (except cannabis) or breath test for alcohol; 2) Current drug or alcohol dependence within the past 30 days as determined by the Composite International Diagnostic Interview (CIDI version 2.1) (WorldHealthOrganization, 1998) using DSM-IV-TR criteria (AmericanPsychiatricAssociation, 1994); 3) A diagnosis of schizophrenia, psychosis, or clinically significant neurological disease including seizures and traumatic brain injury with loss of consciousness > 15 min; or 4) A verbal intelligence quotient (IQ) estimate ≤70 on the Wechsler Test of Adult Reading (WTAR; Psychological Corporation, 2001). Only HIV+ participants who had virologic control on cART with paired plasma and CSF HIV RNA levels < 50 copies/mL were included for the current study. The study was approved by the Institutional Review Board and informed consent was obtained from all participants.

The Memory for Intentions Screening Test (MIST) (Woods et al., 2008b), a standardized 30-minute assessment composed of 8 PM items, was administered to all participants. The MIST contains equally balanced PM items that use a delay of either 2 min or 15 min. Cues were either time-based (e.g., "In 2 minutes, ask me what time this session ends.") or event-based (e.g., "When I hand you a postcard, self-address it.") Response modalities were either verbal (e.g., "Tell me the following") or physical (e.g., "Perform the following action"). A series of word search puzzles served as ongoing distraction tasks that separated PM trials. Raw MIST summary scores were used as the primary PM criterion in all statistical analyses (range = 0–48, with higher scores reflecting better PM performance).

Participants also underwent comprehensive neuropsychological testing for the assessment of HAND according to Frascati criteria (Antinori et al., 2007). The following neurocognitive domains were assessed:

1) Retrospective memory with a) Long-delay discriminability index of the California Verbal Learning Test–Second Edition (CVLT–II; Delis et al., 2000) and b) Logical Memory II subtest of the Wechsler Adult Intelligence Scale- Memory Scales–III (Wechsler, 1997).
2) Attention/working memory with a) Digit Span subtest of the Wechsler Adult Intelligence Scale–Third Edition and b) Trial 1 from the CVLT–II;
3) Executive function with a) total move score from the Tower of London–Drexel test (Culbertson and Zillmer, 1998) and b) Trail Making Test (TMT) Part B; (Reitan and Wolfson, 1985)
4) Speed of information processing with a) Digit Symbol subtest of the WAIS–III and b) TMT Part A;
5) Learning with a) CVLT–II Trials 1–5 total and b) Logical Memory I (LM–I);
6) Verbal fluency with the Action Fluency test (Woods et al., 2005); and
7) Motor skill with Grooved Pegboard Test (Klove, 1963).

Normative values that accounted for age, sex, race, and educational level were used to generate Z scores for each domain. A global clinical rating score was generated from results across these seven domains with a range of 1 (above average) to 9 (severely impaired). Global clinical rating scores ≥5 identified neurocognitive impairment and were used in HAND diagnosis (Woods et al., 2004).

2.2. Laboratory testing

HIV RNA levels from plasma and CSF were measured with a commercial assay (Roche Amplicor v.1.5 with lower limit of detection 50 copies/mL). CSF biomarkers of inflammation and astrocytosis that have been associated with HAND were also measured. These included: CXCL10, an interferon-induced chemokine shown to promote HIV replication in lymphocytes and macrophages (Liu et al., 2011); CCL2, a chemokine responsible for monocyte migration (Dhillon et al., 2008), and s100β, a protein expressed by astrocytes that has an autocrine effect of astrocyte apoptosis (Sen and Belli, 2007). CXCL10 was measured via electrochemiluminescence (Mesoscale Discovery). pTau was measured by Luminex bead array (Invitrogen). S100β was measured by enzyme linked immunosorbent assay (Diasorin). Tryptophan (TRP), Kynurenine (KYN), Picolinic acid (PIC), and QUIN were measured with methods previously described (Jones et al., 2015; Lim et al., 2017). Briefly, TRP and KYN were measured using ultra high performance liquid chromatography (UHPLC), while QUIN and PIC were measured using gas chromatography–mass spectrometry (GC–MS).

2.3. Statistical analyses

For the statistical analysis, variable distributions were inspected for skewness and outliers. As done in previous studies by our group and others, skewness was reduced by natural log transformation to enable use of parametric tests (Anderson et al., 2015; Jessen Krut et al., 2014). Comparisons of HIV+ and negative subjects on continuous variables were performed using *t*-tests. Biomarker comparisons were made without and with adjustment for significant imbalances in demographic profiles of the two groups using linear regression. Comparisons for categorical variables were performed using chi-square tests. Transformation did not substantially improve the distribution of CSF red blood cell (RBC) count so the non-parametric Wilcoxon rank sum test was used to test differences between HIV+ and negative groups. Pearson correlation coefficients were used to test associations between CSF biomarkers and PM as well as CSF biomarkers and pTau. Linear regression was also performed to compare PM and pTau as dependent variables to independent variables that were statistically significant in univariate correlations. We hypothesized that there would be significant relationships between QUIN, pTau, and PM. Comparisons were two-tailed and alpha for statistical significance was set at < 0.05.

3. Results

3.1. Neuropsychological and biomarker results

A total of 66 participants were assessed (43 HIV+ and 23 HIV-negative, see Table 1 for demographic/disease characteristics). HIV+ participants were older and more likely to be men. HIV+ participants were infected for a median of 15 years, median current CD4+ T cell count was 559 cells/μL, and median nadir CD4+ T-cell count was 199 cells/μL. The median duration of the current cART regimen was 17 months and median central nervous system penetration (CPE) score was 7 (interquartile range 6–9). The most commonly prescribed cART