Title: Cerebrospinal Fluid Interferon alpha Levels Correlate with Neurocognitive Impairment in Ambulatory HIV-infected Individuals

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Number of Words:
2308

Disclaimer:
No financial disclosures to report

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Funding:
Emory Medical Care Foundation
NIH K23MH095679
NIH P30 AI050409 (Emory Center for AIDS Research)
The Knut and Alice Wallenberg Foundation

The Torsten Söderberg Foundation

The Swedish Research Council

The European Research Council

This work was presented in part as: CSF Interferon Alpha Levels Inversely Correlate with Processing in HIV-infected Subjects with Cognitive Complaints. Poster Abstract 437, 20th Conference on Retroviruses and Opportunistic Infections (CROI), Atlanta, Georgia, 2013.

Abstract (JNV format):

HIV-associated neurocognitive disorders (HAND) continue to be common, are associated with increased morbidity and mortality, but the underlying mechanisms in the combination antiretroviral (cART) era are not fully understood. Interferon alpha (IFNα) is an antiviral cytokine that was found to be elevated in the cerebrospinal fluid (CSF) among individuals with advanced HIV-associated dementia in the pre-cART era. In this small cross-sectional study, we investigated the association between IFNα and neurocognitive performance in ambulatory HIV-infected individuals with milder impairment. An eight test neuropsychological battery representing multiple cognitive domains was administered. In addition to individual demographically adjusted scores, a composite neuropsychological score (NPT-8) was calculated. IFNα and CSF neurofilament light chain (NFL) levels were measured using enzyme linked immunosorbent assay (ELISA). There were 15 chronically infected participants with a history of significant immunocompromise (median nadir CD4+ of 49 cells/microliter). Most participants were neurocognitively impaired (mean Global Deficit Score of 0.86). CSF IFNα negatively correlated with three individual tests (Trailmaking A, Trailmaking B, and Stroop Color-word) as well as the composite NPT-8 score ($r = -0.6360$, $p = 0.011$). Additionally, CSF IFNα correlated strongly with CSF NFL ($rho = 0.748$, $p= 0.0013$). These results extend findings from individuals with severe HIV-associated dementia in the pre-cART era and suggest that IFNα, a known neurotoxin, could continue to play a role in HAND pathogenesis in the cART era. Further investigation, including research on targeted anti-IFNα therapy as a therapeutic modality for individuals with HAND, is indicated.

Background

HIV-associated neurocognitive disorders (HAND) continue to be a major problem in the era of combination antiretroviral therapy (cART). Studies in mostly cART-treated populations have shown that HAND is present in 25-50% of HIV-infected individuals.[1, 2] In addition to being highly prevalent, HAND is associated with multiple adverse clinical outcomes, including decreased quality of life and increased mortality.[3, 4] Yet, the pathogenesis of HAND, particularly in the setting of cART, has not been fully elucidated. A number of soluble biomarkers have been studied and are associated with the presence of HAND. Interestingly, many of these biomarkers appear to represent diverse pathological pathways (neopterin reflecting monocyte activation, neurofilament light chain reflecting neuronal degeneration, and others).[5-7] Therefore, more research is needed to identify other biomarkers that could contribute to a more comprehensive picture of HAND pathogenesis. Additionally, given that no treatments other than cART have been found to ameliorate HAND[8] (and even with cART the disorder is often not completely eradicated), new therapeutic targets are needed.

Interferon-alpha (IFNα) is an antiviral cytokine found to be the only type I interferon that is elevated in the plasma of HIV-infected individuals compared to uninfected controls.[9] IFNα has been shown to have a direct neurotoxic role in animal models as well as in humans. In a murine model of HIV encephalitis, mice develop altered behavior and express increased IFNα in the brain.[10] Blockage of IFNα in the setting of this model has been shown to ameliorate encephalitis.[11] In humans, IFNα has been associated with significant neuropsychiatric toxicity when used for the treatment of chronic hepatitis C infection and other diseases.[12] While found to be undetectable in >90% of normal individuals,[13] CSF IFNα levels were shown to be significantly elevated among individuals with HIV-associated dementia in the pre-cART era.[14]

However, given that HAND during the cART era is mostly comprised of milder impairment,[1] further research on the role of IFNα is indicated. Therefore, we sought to measure CSF IFNα in a cohort of predominantly cART experienced individuals to determine its relationship with neurocognitive (NC) performance.

Methods

Participants

HIV-infected adult outpatients who reported changes in memory were enrolled between March 2011 and November 2011 at the Emory University Center for AIDS Research (CFAR) clinical core site in Atlanta, Georgia. In order to minimize confounding comorbidities, potential participants were excluded from the study for any of the following: 1) history of any neurologic disease known to effect memory (including stroke, malignancy involving the central nervous system, traumatic brain injury, and AIDS-related opportunistic infection of the central nervous system); 2) ongoing substance use (marijuana use in the last 7 days OR cocaine, heroin, methamphetamine, or other non-marijuana illicit drug use in the last 30 days); 3) Heavy alcohol consumption in the last 30 days (defined as >7 drinks per week for women and >14 drinks per week for men); or 4) serious mental illness including schizophrenia and bipolar disorder (depression was not excluded if participants were well controlled on treatment). Participants were also screened for hypothyroidism (with serum TSH level), vitamin B12 deficiency (with serum B12 level), and cryptococcal disease if CD4+ T-cell count was <100 cells/μl (with serum cryptococcal antigen) and excluded if any were found to be abnormal. Participants with a history of treated syphilis and a persistently positive RPR titer of 1:4 or less were eligible for the study if there was a decrease in RPR of at least fourfold at six months after treatment and there were no

neurological symptoms at initial syphilis presentation. Lastly, participants were excluded in the event that severe cognitive symptoms had occurred precipitously in the last 30 days in order for further medical workup to be undertaken.

Neuropsychological Testing

The neuropsychological (NP) battery included the HIV dementia scale as well as the following eight tests that are used commonly in studies of cognition during HIV infection:[15] 1) Trailmaking Part A; 2) Trailmaking Part B; 3) Hopkins Verbal Learning Test total recall; 4) Hopkins Verbal Learning Test delayed recall; 5) Grooved Pegboard (dominant hand); 6) Stroop Color/Word; 7) Letter Fluency (Controlled Oral Word Association Test) and 8) Animal Fluency. These tests were selected in order to examine at least five domains as recommended in the most recent nosology of HAND criteria.[16] The tests were administered by study staff after intensive training and supervision by an experienced, board certified neuropsychologist (DL). Test scores were adjusted for demographic characteristics using norms published by Heaton et al[17] that account for age, sex, and race (with the exception of HVLT and Stroop tests, for which adjusted values were not available) to arrive at individual T scores. A composite neuropsychological test score (NPT-8) was then calculated by averaging the eight individual T scores, as performed in other studies of neurocognition in HIV. Global Deficit Score (GDS), a validated measure of neurocognitive impairment in HIV based on demographically corrected T scores, was also calculated and as per published literature a score of ≥ 0.5 was indicative of neurocognitive impairment.[18] The study was approved by the Emory University Institutional Review Board and written consent was obtained from all subjects.

Blood and Cerebrospinal Fluid Evaluations

On the same day of NP testing, paired blood and cerebrospinal fluid (CSF) samples were obtained, processed and stored at -80 degrees centigrade. Plasma and CSF HIV RNA levels were quantified with the Abbott laboratories Real Time HIV-1 assay (reverse transcriptase polymerase chain reaction) using the Abbott m2000 system. Lowest limit of HIV detection was 40 copies/ml. IFNα levels were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits (PBL Assay Science, Piscataway NJ, USA) according to the manufacturer's instructions. All samples and standards were measured in triplicates as picograms/ milliter (pg/ml). CSF neurofilament light chain (NFL), an established marker of neuronal injury,[7] was also measured by ELISA (UmanDiagnostics, Umea, Sweden). This assay has a lower limit of quantification of 50 pg/ml and intra-assay coefficients of variation below 10%. All samples were analyzed as single samples in one round of experiments using one batch of reagents by board-certified laboratory technicians who were blinded to clinical data. Other studies including CD4+ T-lymphocyte counts were performed by the hospital clinical laboratories. In addition to the HIV-infected participant samples, the cerebrospinal fluid samples from four HIV-seronegative individuals were included for IFNα testing.

Statistical analyses

Statistical analyses were performed with SAS software. Normality was assessed with the Shapiro-Wilk test. Differences between non-normal groups were calculated with the Wilcoxon rank-sum test. For correlations, non-normal variables were log10 transformed for the Pearson correlation test (r). If log10 transformation did not yield values that met criteria for normality, the Spearman correlation test (rho) was used. Alpha levels were two-tailed and a p value of <0.05 was considered statistically significant. Analyses with multiple p values of < 0.05 were

corrected for multiple comparisons using the Benjamini-Hochberg false discovery rate procedure.

Results

A total of 15 HIV-infected participants were enrolled. Median age (table 1) was 49 years, 80% were men, and 73.3% were African-American. Most subjects had a long history (median 8 years) of HIV and a history of significant immunocompromise (median CD4+ nadir of 49 cells/µl and median current CD4+ of 62 cells/µl). The majority of subjects (60%) were cART experienced and 20% were currently on cART with undetectable plasma and CSF HIV RNA < 40 copies/ml. Mean NPT-8 score was 43.7 (standard deviation 9.34) and mean GDS of 0.86 (standard deviation 0.995). 9 of 15 subjects (60%) met criteria for neurocognitive impairment by GDS ≥0.5 while 4 of 15 (26.7%) had more severe impairment with GDS ≥1.5. There were two healthy HIV-seronegative controls (one 57 year old female with CSF IFNα level of 2.14 picograms [pg]/ml and one 52 year old female with CSF IFNα 1.19 pg/ml) as well as two HIV-seronegative individuals with Alzheimer's disease (one 64 year old male with CSF IFNα 5.95 pg/ml and one 73 year old female with CSF IFNα 3.1 pg/ml). CSF IFNα level was significantly higher (p=0.012) in the participants with HIV (median 7.86 pg/ml, overall range 2.62-45.95) compared to the participants without HIV. When limiting the comparison to the two Alzheimer's disease participants, HIV-infected participants tended to have higher CSF IFNα but this difference was not statistically significant (p= 0.13).

In the HIV-infected participants, there was no significant difference (p=0.94) in plasma IFNα levels between participants on cART with undetectable plasma/CSF HIV RNA (median 34.1 pg/ml, interquartile range [IQR] 3.07 – 98.73) and participants off cART (median 18.9

pg/ml, IQR 2.07-115.9). Similarly, CSF IFNα levels did not significantly differ (p=0.31) between participants on cART with undetectable plasma/CSF HIV RNA (median 7.38 pg/ml, IQR 4.52 – 7.86) and participants off cART (median 8.34 pg/ml, IQR 6.67 – 16.55). There was no statistical difference (p=0.28) in plasma IFNα among participants with either active hepatitis B or C (median 39.9 pg/ml, IQR 18.9 - 209.73) versus participants without (15.9 pg/ml, IQR 2.07 - 98.73). Similarly, there was no statistical difference (p=0.69) in CSF IFNα levels among participants with either active hepatitis B or C (median 9.5 pg/ml, IQR 6.67 – 37.38) versus participants without (median 7.86 pg/ml, IQR 4.52 – 12.62). Median CSF NFL level in the HIV-infected participant group as a whole was 563 pg/ml (overall range 293-12233). CSF NFL correlated significantly with CSF IFNα (rho = 0.748, p= 0.0013).

There were multiple negative correlations between CSF IFNα levels and neurocognitive performance that were statistically significant (table 2). CSF IFNα correlated negatively with composite NPT-8 score (r = -0.6360 p = 0.011). In terms of individual NP tests, CSF IFNα correlated negatively with Trailmaking test A (r = -0.7353, p = 0.0018, Figure 1), Trailmaking test B (r = -0.6766, p = 0.0056), and Stroop color-word test (r = -0.6649, p = 0.0095). These three correlations remained statistically significant after false discovery rate correction (p values= 0.014, 0.022, and 0.025 respectively). There was only one significant correlation with plasma IFNα (Trailmaking test A, r = -0.5608, p = 0.0369), but this correlation became non-significant (p = 0.28) after false discovery rate correction.

When comparing participants with GDS ≥0.5 versus < 0.5, there was no significant difference in CSF IFNα levels (median 8.81 pg/ml [IQR 5.24-19.5] versus median 7.86 [IQR 5.95-9.05], p=0.59) or in plasma IFNα levels (median 37 pg/ml [IQR 5.53-175.4] versus median 11.65 pg/ml [IQR 2.3-103.02], p=0.61). However, when grouped by severe impairment (GDS

≥1.5 versus < 1.5), participants with severe impairment had significantly higher CSF IFNα levels (median 19.53 pg/ml [IQR 10.0-39.76] versus median 7.86 pg/ml [IQR 4.52-8.81], p=0.049). Participants with GDS ≥1.5 versus < 1.5 tended to have higher plasma IFNα levels (median 94.4 pg/ml [IQR 39.9-202.4] versus median 15.9 pg/ml [IQR 2.07-98.73]) but this difference was not statistically significant (p=0.16).

Discussion

Given the high prevalence of HAND in the cART era, there is an ongoing need to better understand the mechanisms behind these disorders. CSF levels of IFNα, an antiviral cytokine with neurotoxic properties, were found in the pre-cART era by members of our group to be significantly elevated among individuals with HIV-associated dementia.[14] However, it is unclear if this cytokine remains associated with HAND in the modern HIV treatment era, in which most affected individuals have relatively milder forms of NC impairment. While the present study represents a small sample size, the study population was comprised of ambulatory outpatients who did not have advanced dementia. Our results show that CSF IFNα levels negatively correlate with multiple measures of neurocognitive function, including a composite score that reflects global performance. These correlations may have been driven by participants with more significant (a GDS of ≥1.5 as suggested by other studies)[19] impairment, who had significantly higher CSF IFNα levels. Of note, the individual tests (Trailmaking and Stroop) that were negatively associated with CSF IFNα and appeared to underpin the overall negative association with composite performance are generally regarded as tests of executive function and processing speed. These contrast with the other individual tests in our battery (which evaluated memory, fluency, and motor skill) that were not associated with CSF IFNα. Our findings suggest that the

detrimental effects of IFNα may be most specific to brain regions that are linked to executive function (such as the frontal lobes and associated subcortical tracts) and processing speed (such as white matter), an interpretation supported by the correlation of CSF IFNα with CSF NFL, an established marker of injury to large caliber myelinated axons in HIV (refs: Gisslén M et al. BMC Neurol. 2009 Dec 22;9:63; Peterson J et al., PLoS One. 2014 Dec 26;9(12):e116081), as well as in other CNS disorders (refs: Skillbäck T et al. Neurology. 2014 Nov 18;83(21):1945-53; Zetterberg H et al., JAMA Neurol. 2016 Jan 1;73(1):60-7).

However, we acknowledge that the mechanism of IFNα-induced neurotoxicity is not fully understood at this time.[12, 20] IFNα initiates an antiviral response by binding to the type I IFN receptor (IFNAR) with subsequent activation of the JAK/STAT pathway. However, blocking the IFNAR only partially prevents neurotoxicity caused by IFNα, suggesting that the cellular signaling involved in IFNα neurotoxicity is more complex than binding to its own receptor. The NMDA receptor (NMDAR) has also been linked to IFNα toxicity in clinical and *in vitro* studies.[21] Interestingly, other neurotoxins that have been implicated in the pathogenesis of HAND also appear to act through the NMDAR.[22] Targeting NMDAR mediated excitotoxicity may be a common pathway and is a possible candidate for HAND therapeutics that would complement cART.

We acknowledge the limitations of the study, including the small sample size. We had very few HIV-seronegative controls, though previous research has shown that CSF IFNα is undetectable or near undetectable in the vast majority of healthy individuals.[13] Two of these HIV seronegative subjects had Alzheimer's disease, and while these individuals appeared to have lower CSF IFNα levels than the HIV-infected individuals, we were not able to reject the null hypothesis that there was no statistical difference between Alzheimer's and HIV groups. It is

very likely that our study was under-powered to effectively address this question. Further studies on individuals with Alzheimer's disease would be needed to determine if CSF IFNα levels in this group are different than in individuals without neurologic disease.

We also acknowledge that one third of the subjects in the study had either chronic hepatitis B or C. Since the presence of chronic hepatitis has been shown to effect systemic interferon alpha levels,[23] the inclusion of these individuals may have influenced our results. While the majority of subjects in the study were cART experienced, a minority were actually on cART at the time of the study with suppressed plasma and CSF HIV RNA levels. While we did not find that plasma or CSF IFNα levels were lower in these individuals on cART, the sample size of these subjects was too small to perform an analysis that excluded subjects off cART. Ideally a larger study would be performed focusing on patients with neurocognitive impairment despite virologic suppression on cART. Given the persistence of HAND in the cART era, more research is needed in order to determine the relationship between IFNα and neurocognitive performance in HIV-infected individuals.

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Table 1: Participant demographic and disease characteristics (see box for abbreviations)

Variable **N = 15 unless otherwise stated**	**Frequency (%)** **or median (IQR; range)** **or mean [Standard deviation]**
Age in years	49(43-52; 35-59)
Sex	
Male	12 (80%)
Female	3 (20%)
Race	
African-American	11 (73.3%)
Caucasian	4 (26.7%)
Years of HIV diagnosis	8 (2-14; <1-25)
Co-morbidities	
Current cigarette smoker	9 (60%)
Hepatitis C positive	3 (20%)
Hypertension	2 (13.3%)
Depression	2 (13.3%)
Hepatitis B positive	1 (6.7%)
cART naïve	6 (40%)
cART experienced but off treatment	6 (40%)
Currently on cART	3 (20%)

Laboratory results	
CD4 count (cells/µl)	62 (29-201; 10-922)
CD4%	10 (4-21; 1-39)
CD4 nadir (n=13)	49 (20-102.5; 10-153)
Log Plasma HIV (detectable n=12)	4.76 (3.92-5.34; 3.6-5.82)
Hemoglobin (g/dl)	12.8 (12-14.2; 9.4-15.7)
Creatinine (mg/dl)	1.0 (0.8-1.4; 0.7-1.6)
Plasma IFN-α (pg/ml, n=14)	26.5 (2.82-103.02; 0-209.73)
CSF WBC	0 (0-4; 0-12)
CSF RBC	0 (0-1 ;0-58)
CSF Protein	38.5 (33.25-52.75; 15-95)
Log CSF HIV (detectable n= 12)	3.09 (2.70-4.16; 1.61-5.25)
CSF IFN-α (pg/ml)	7.86 (6.43-12.62; 2.62-45.95)
CSF NFL (ng/liter)	563 (487-826; 293-12233)
Neuropsychological testing	
HIV dementia scale score	11.47 [3.91]
NPT-8	43.7 [9.34]
GDS	0.86 [0.995]

IQR = interquartile range; HIV = human immunodeficiency virus; cART = combination antiretroviral therapy; CD = cluster of differentiation; µl= microliters; g = grams; dl = deciliter; mg = milligrams; pg= picograms; CSF = cerebrospinal fluid; WBC = white blood cell count; RBC = red blood cell count; IFNα = interferon alpha; NFL= Neurofilament light chain; ng= nanograms; NPT

Table 2: Correlations between IFNα and Neurocognitive (NC) Performance

NC performance measure	CSF IFNα Pearson correlation with log 10 transformation (p value)	Plasma IFNα Pearson correlation with log 10 transformation (p value)
NPT-8	-0.6729 (0.0084)	NS
Trails A	-0.7353 (0.0018)	-0.5608 (0.0369)
Trails B	-0.6766 (0.0056)	NS
HVLT total	NS	NS
HVLT delay	NS	NS
Peg dominant	NS	NS
Stroop Color word	-0.6649 (0.0095)	NS
Letter Fluency	NS	NS
Animal Fluency	NS	NS

Table 2 Abbreviations: CSF = cerebrospinal fluid; IFNα = interferon alpha; NPT = composite neuropsychological test score; NS = not significant; GDS = global deficit score; HVLT = Hopkins Verbal Learning Test

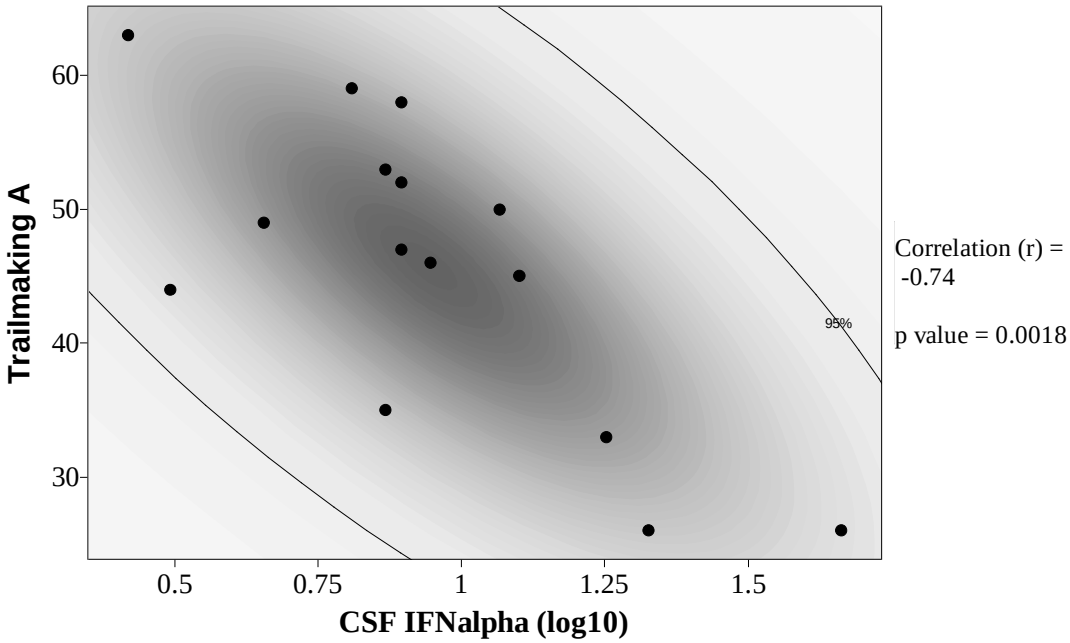
Trailmaking A
60
50
40
30
0.5
0.75
1
1.25
1.5
CSF IFNalpha (log10)
95%
Correlation (r) = -0.74
p value = 0.0018

Figure 1