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Plasma soluble CD163 is associated with postmortem brain pathology in human immunodeficiency virus infection

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Abstract

Objective—Higher plasma soluble CD163 (sCD163), shed by monocytes and macrophages, correlates with neurocognitive impairment in human immunodeficiency virus (HIV) infection. We hypothesized that higher antemortem plasma or cerebrospinal fluid sCD163 would be associated with greater postmortem neurodegeneration and/or microgliosis.

Design—Retrospective, postmortem observational study.

Methods—We measured sCD163 levels in antemortem plasma (n=54) and cerebrospinal fluid (n=32) samples from 74 HIV^+ participants (median 5 months before death) who donated their brains to research at autopsy. Postmortem, we quantified markers of synaptodendritic damage (microtubule-associated protein 2 [MAP2], synaptophysin [SYP]), microgliosis (HLA-DR, ionized calcium binding adaptor molecule 1), astrocytosis (glial fibrillary acidic protein) and impaired protein clearance (beta-amyloid) in frontal cortex, hippocampus, putamen, and internal capsule. Multivariable least-squares regression was used to evaluate the association between plasma or cerebrospinal fluid sCD163 and histological measures, correcting for multiple comparisons.

Results—Higher plasma sCD163 was associated with lower MAP2 in frontal cortex (B=−0.23, 95% CI −0.41 to −0.06, p=0.04), putamen (B=0.32, 95% CI −0.52 to −0.12, p=0.02), and

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hippocampus (B=−0.23, 95% CI −0.35 to −0.10, p=0.01), and with lower SYP in hippocampus (B=−0.25, 95% CI −0.42 to −0.03, p=0.02) but not putamen or frontal cortex (p>0.05). Higher plasma sCD163 was associated with higher HLA-DR in putamen (B=0.17, 95% CI 0.08 to 0.26, p = 0.008). Cerebrospinal fluid sCD163 was not associated with any histological measure (p>0.05).

Conclusions—Higher plasma sCD163 in life is associated with greater synaptodendritic damage and microglial activation in cortical and subcortical brain regions.

Keywords

HIV; neurodegenerative disorders; mild cognitive impairment; antiretroviral therapy; acquired immunodeficiency syndrome; brain

INTRODUCTION

Mild and moderate forms of HIV-associated neurocognitive disorders (HAND) persist despite effective combination antiretroviral therapy (cART) [1,2]. Multiple etiologies have been proposed to underlie HAND, including ongoing inflammatory and dysregulatory effects of latent HIV in the brain, cerebrospinal fluid (CSF) viral escape, and possible neurotoxic effects of cART [2–5]. The neuropathological substrate of HAND may include synaptodendritic damage and/or persistent immunologic activation [6]. Indeed, synaptodendritic damage as measured by synaptophysin (SYP, a marker of presynaptic terminals) and microtubule-associated protein 2 (MAP2, a marker of neuronal somata and dendrites), correlates with measures of neurocognitive impairment [7, 8].

Reliable CSF or plasma biomarkers that correlate with HIV-related neurologic damage have remained elusive, though many have been proposed [9–16]. The search has focused on correlating blood or CSF proteins with clinical measures of neurocognitive impairment. One of the most promising candidate biomarkers is plasma soluble CD163 (sCD163), a marker of activated macrophages that is elevated in HIV infection and declines in parallel with peripheral HIV viral load [17]. In simian immunodeficiency virus infection, plasma sCD163 levels correlates with monocyte recruitment from bone marrow, progression to AIDS, and severity of encephalitis [18]. In humans, plasma but not CSF sCD163 is elevated in virally suppressed HIV seropositive (HIV^+) patients with HAND [19]. The reason for this difference between plasma and CSF sCD163 is unclear, as it is unknown whether CNS monocytes shed sCD163 into the CSF as readily as peripheral circulating monocytes shed into plasma. The presence of HIV-DNA in peripheral monocytes has been linked to HAND, providing a possible link between peripheral immune activation and CNS damage. [20–22]

Few studies have attempted to validate candidate biomarkers by linking them to the neuropathological features underlying HAND. In this study of HIV^+ individuals, we hypothesized that higher antemortem plasma or CSF sCD163 levels are associated with higher postmortem neuropathological measures of neurodegeneration, microglial activation, and impaired protein clearance. We further hypothesized that higher sCD163 would be associated with worse neurocognitive performance on a standardized battery of neurocognitive tests.

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METHODS

Participants

We studied 74 individuals enrolled in either the California NeuroAIDS Tissue Network (CNTN) or National Neurological AIDS Bank (NNAB) who died between August 1999 and January 2012. Inclusion criteria were HIV$^+$ status, age greater than 18 years, and classified as either neurologically normal or diagnosed with HAND within one year of death [1]. Exclusion criteria were neurocognitive impairment from a cause other than HIV, pre- or postmortem evidence of neurological disease unrelated to HIV (e.g. cerebral neoplasm or cerebrovascular accident), history of progressive multifocal leukoencephalopathy or toxoplasmosis, and diagnosis of substance dependence within one year of death.

Neurocognitive testing

Domain-specific neuropsychological clinical ratings were determined using demographically corrected T-scores from a standardized, comprehensive neuropsychological evaluation administered within one year of death. Scores ranged from one to nine (most impaired) with scores greater than five indicating clinically significant impairment, as previously described [3, 8, 20]. The neuropsychological evaluation emphasizes tests that are sensitive to the particular deficits observed in HIV infection and includes seven domains: verbal fluency, speed of information processing, learning, memory, executive functions, attention and working memory, and motor skills. Domain-specific scores are then summarized as a global clinical rating, which has been shown to correlate with synaptodendritic loss [8].

HIV measures and biomarkers

HIV RNA viral load measurement was performed on peripheral blood samples drawn within one year of death (Roche Amplicor Assay, lower limit of quantitation 50 copies/mL). CD4$^+$ T-cell counts were obtained by flow cytometry a median of 23 months before death (Table 2). In a subset of 38 patients, frontal cortex HIV RNA and DNA levels were measured by PCR as previously described [24]. Duration of HIV infection and nadir CD4$^+$ T-cell counts were obtained by self-report. sCD163 was detected in plasma and CSF samples obtained by routine phlebotomy and lumbar puncture prior to death using ELISA (Trillium Diagnostics; median time to death 5 months for plasma, 6 months for CSF; Table 2).

Immunohistochemistry

Immunohistochemical characterization was performed on sections of dorsolateral mid-frontal cortex (layers II-VI) and subcortical white matter, hippocampal CA1, putamen, and internal capsule.

SYP and MAP2: Fresh tissue blocks from hippocampus, putamen, and internal capsule were fixed with 4% paraformaldehyde and sectioned to 40 μm with a vibratome (Leica, Vienna). Free-floating tissue sections were immunostained with mouse monoclonal primary antibodies against MAP2 (clone 5F9, # 05-346, EMD Millipore, Billerica, MA, USA, 1:20) or SYP (clone SY38, # MAB5258, EMD Millipore, Billerica, MA, USA, 1:10). For frontal cortex, fresh tissue blocks were embedded in paraffin before immunostaining and were

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treated with DAB after incubation with biotinylated secondary antibodies. For the gray matter of each brain region, three microscopic fields were imaged with a confocal microscope (MRC-1024, Bio-Rad, Hercules, CA, USA) adjusting contrast and gain to obtain images with pixel intensity within a linear range. Quantification of the number of SYP^+ presynaptic terminals per 100 μm^2 and percentage neuropil occupied by $MAP2^+$ dendrites was performed with IMAGE software as previously described [8, 22].

HLA-DR, ionized calcium binding adaptor molecule-1 (IBA-1), glial fibrillary acidic protein (GFAP), and beta-amyloid: Formalin-fixed and paraffin-embedded sections (5 μm thick) from each brain region were immunostained with antibodies against HLA-DR (clone LN3, # 14-9956, eBioscience, San Diego, CA, USA, 1:1000), IBA-1 (# 019-19741, Wako, Richmond, VA, USA; 1:1000), beta-amyloid (clone 4G8, # SIG-39220, Covance, Princeton, NY, USA; 1:20,000) and GFAP (# Z0344, DAKO, Carpenteria, CA, USA; 1:1000) [25]. Sections were scanned with a microscope slide scanner (Aperio ScanScope GL, Leica Biosystems, Buffalo Grove, IL, USA). We determined immunoreactivity per unit area for HLA-DR, IBA-1, and GFAP in each brain region as previously described [22, 23]. For beta-amyloid, we performed semi-quantification of beta-amyloid plaques, adapted from standard CERAD criteria [27]. Quantifications from frontal cortex gray matter, putamen, and hippocampal CA1 were averaged to provide a composite whole-brain score.

Covariates and statistical analysis

Screened covariates included age at death, gender, ethnicity (white vs. non-white), nadir $CD4^+$ T-cell count, history of smoking, lifetime major depression, lifetime alcohol abuse, lifetime stimulant abuse, hypertension, diabetes mellitus type II, hyperlipidemia, end-stage liver disease, chronic renal disease, chronic obstructive pulmonary disease, cerebrovascular disease, lipodystrophy, non-AIDS defining cancer, and brain histological findings of cryptococcosis or cerebral CMV infection. Medical comorbidities and nadir $CD4^+$ T-cell counts were self-reported by participants.

Covariates were included in multivariable models if they were associated with the histological outcome in univariable least-squares regression at $p < 0.25$. Plasma or CSF sCD163 measurement interval to death was included in every model regardless of association with the histological outcome. One individual with plasma sCD163 > 5 standard deviations above the mean was excluded from the analyses. Standard least-squares regression was used for multivariable analyses. Significant associations were further tested with false discovery rate (FDR) correction [28]. Matched-pair analysis was used to compare plasma and CSF sCD163 in each participant. Correlations were performed with Spearman's method. Univariable least-squares regression was used to evaluate associations between CSF sCD163 and histological markers. Comparison of CSF and plasma sCD163 across groups was performed with two-tailed t-test on log-transformed data. All statistical analyses were performed with JMP 11 (SAS). Correlation coefficients for plasma sCD163 were calculated for 100 ng/mL increments.

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RESULTS

Participants

The cohort comprised 74 individuals who were primarily male (84%) and white (69%) with a mean age at death of 47 (range 27–68) (Table 1). Many reported lifetime alcohol abuse (53%) or stimulant abuse (38%) and we observed a high prevalence of HAND within one year of death (76%). There was poor viral control in the years preceding death, with median blood viral load of 16700 copies/mL in the last year of life and median $CD4^+$ T-cell count of 53 cells/mm^3 (measured a median of 23 months prior to death) (Table 2). Only seven of 53 individuals (13%) with plasma viral load data had undetectable viral load at the last antemortem visit. Histological evidence of active CNS infection (HIVE, CMV, or cryptococcosis) was observed in a small minority of individuals (1–4%, Table 2).

Mean plasma sCD163 levels were higher than CSF sCD163 within individuals (1082 ng/mL vs. 43 ng/mL, n = 26, $p < 0.0001$) and trended toward correlation with each other ($\rho = 0.34$, n = 26, $p = 0.08$). There was no difference between those with HAND vs. neurocognitively normal in plasma sCD163 (t = 1.5, $p = 0.14$) or CSF sCD163 (t = 0.1 $p = 0.7$). Neither plasma nor CSF sCD163 were correlated with global or domain-specific clinical ratings in neuropsychological testing ($p > 0.20$ for all pairwise correlations). Higher global clinical rating (indicating worse impairment) was associated with lower SYP and lower MAP2 in putamen (SYP: $\rho = -0.76$, $p < 0.001$; MAP2: $\rho = -0.77$, $p < 0.001$), hippocampus (SYP: $\rho = -0.59$, $p < 0.001$; MAP2: $\rho = -0.62$, $p < 0.001$), and frontal cortex (SYP: $\rho = -0.31$, $p = 0.01$; MAP2: $\rho = -0.38$, $p = 0.001$). Global clinical ratings were not associated with IBA-1, GFAP, HLA-DR, or beta-amyloid.

Regression analyses

Results of multivariable models for plasma sCD163 are presented in Table 3. Higher plasma sCD163 was associated with lower MAP2 in dorsolateral frontal cortex (B = –0.23, 95% CI –0.41 to –0.06, $p = 0.007$), putamen (B = –0.32, 95% CI –0.52 to –0.12, $p = 0.004$), and hippocampus (B = –0.23, 95% CI –0.35 to –0.10, $p = 0.001$) and these associations remained significant after correcting for multiple comparisons. Higher plasma sCD163 was associated with lower SYP in hippocampus (B = –0.25, 95% CI –0.42 to –0.03, $p = 0.003$) and putamen (B = –0.25, 95% CI –0.39 to –0.10, $p = 0.02$), though the latter was not significant after correction for multiple comparisons ($p > 0.05$). Higher plasma sCD163 was associated with higher HLA-DR immunoreactivity in putamen (B = 0.17, 95% CI 0.08 to 0.26, $p < 0.001$) and when composited across brain regions (B = 0.11, 95% CI 0.05 to 0.17, $p < 0.001$). Plasma sCD163 was not significant in models for other markers (GFAP, IBA-1, beta-amyloid) in each brain region. In univariable regression, CSF sCD163 was not associated with HLA-DR, GFAP, IBA-1, beta-amyloid, MAP2, or SYP in any brain region examined ($p > 0.05$ for all).

Effect of HIV disease variables

Adding antemortem plasma HIV viral loads or frontal cortex HIV RNA levels to each multivariable regression model for SYP, MAP2 and HLA-DR did not affect the significance of the plasma sCD163 parameter ($p < 0.05$) with the exception of adding blood viral load to

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the model for putamen SYP (plasma sCD163; $p = 0.22$). There was no difference in mean CSF or plasma sCD163 among those with detectable vs. undetectable viral load at the last clinical visit (CSF: $p = 0.2$; plasma: $p = 0.5$). Plasma sCD163 levels were not correlated with frontal cortex HIV RNA ($p = 0.4$) or DNA ($p = 0.5$) ($n = 26$ for both). CSF sCD163 levels were correlated with frontal cortex HIV DNA ($\rho = 0.69$, $p = 0.001$) but not RNA ($p = 0.07$) ($n = 13$ for both).

DISCUSSION

Here we show that elevated antemortem plasma sCD163 is associated with neuropathological measures proposed to underlie HAND. Prior studies have shown that plasma sCD163 is increased in HIV infection, decreases in parallel with viral load, and is elevated in HIV^+ individuals with HAND compared to the cognitively unimpaired [17, 19]. Interestingly, upon achieving complete viral suppression, sCD163 decreases but remains elevated in HIV^+ individuals compared to HIV seronegative controls which may reflect persistent immune activation [17]. CSF sCD163 does not appear to bear the same relationship as plasma sCD163 to HIV activity and cognitive impairment [19]. Further, MAP2 and SYP in cortex, putamen, and hippocampus robustly correlate with neurocognitive impairment in HIV [8, 21, 26]. This study supports these findings by linking elevated plasma but not CSF sCD163 to lower dendrite density (MAP2) in frontal cortex, putamen, and hippocampus, lower synapse density (SYP) in hippocampus and putamen (though the latter was not significant after adjustment for multiple comparisons), and greater microglial activation (HLA-DR) in putamen.

Cognitive impairment in HIV lies along a continuum of severity, from mild cognitive impairment to severe dementia. While frank encephalitis and severe cognitive impairment were more common in the pre-cART era, mild and mild-to-moderate forms of cognitive impairment are now more prevalent and suppression of CNS viral replication is common. The pathogenesis of HAND in the absence of severe encephalitis is an area of active research. Prominent theories include ongoing inflammatory and dysregulatory effects of latent HIV in the brain, CSF viral escape, and direct neurotoxic effects of cART [2–6, 27]. By linking synaptodendritic damage with plasma sCD163 and hippocampal HLA-DR, both markers of microglial/macrophage activation, this study supports chronic immune activation as an underlying factor in HAND pathogenesis.

Although most participants did not have adequate viral control in the last year of life, there was little evidence that the link between plasma sCD163 and neuropathology was mediated by active HIV replication. First, only 2 of 74 individuals had evidence of HIVE on postmortem neuropathology, suggesting a low rate of severe CNS infection. Second, antemortem peripheral viral loads and postmortem frontal cortex HIV RNA levels had no mediating effect on the relationship between plasma sCD163 and our neuropathological outcomes in multivariable models. Finally, plasma sCD163 was not correlated with either peripheral HIV viral loads or frontal cortex HIV RNA levels. The link between plasma sCD163 and neurologic damage may thus be invariant to peripheral or CNS viral burden, though our investigations are complicated by the fact that plasma sCD163, HIV viral load, and frontal cortex HIV levels were not measured simultaneously.

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Our study was constrained by a limited sample size ($n = 74$, with most analyses in subsets); however, this is a large sample for a postmortem study of this type. Comorbidities were self-reported, likely introducing recall bias. As noted above, most participants had uncontrolled HIV viral load before death, which may limit generalizability to the contemporary population of treated HIV$^+$ individuals. Finally, in our sample plasma sCD163 was not correlated to cognitive impairment, a puzzling finding that is at odds with previous research [19]. This previous work has focused on patients with long-term viral suppression; thus plasma sCD163 may have a different relationship to cognitive impairment in those with uncontrolled disease [19]. It is also possible that our study was underpowered to detect a correlation with cognitive impairment scores, whereas neuropathological damage might be a more sensitive measure of the underlying disease process. Finally, sCD163 was not measured at the same time as the neurocognitive testing battery, introducing a temporal confounder that likely obscured the link between sCD163 and cognitive impairment. We chose to use antemortem over postmortem sCD163 measurements due to the potentially severe confounding of changes in inflammatory marker levels following death and during the dying process [31–33]. Finally, the varying time discrepancy from plasma sCD163 measurement to death is a significant limitation of our study, though we attempted to address this weakness by including the time lag as a covariate in each multivariable model.

HAND continues to be an important problem facing patients living with HIV. Finding reliable and convenient biomarkers of HIV-associated neurologic damage is critical to improving care and quality of life for this population. Plasma sCD163 has emerged as a leading candidate for the role. This study links plasma sCD163 to the neurodegenerative phenotype proposed to underlie HAND, a crucial step in the validation of this candidate biomarker.

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A.K.B, D.J.M, A.J.L, R.J.E, and I.G. conceptualized and designed the study. T.H.B., J.R.L., and R.J.E. performed plasma and CSF biomarker assays. V.S., C.L.A., and E.M. performed histological analyses. A.K.B. wrote the manuscript. B.G. provided administrative support and data management.

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Table 1

Demographics and comorbidities.

Age, years (mean) (SD, range, n)	47 (9, 27–68, 74)
Gender: male	62/74 (84%)
Ethnicity: white	51/74 (69%)
Major depression	1/64 (1.5%)
Alcohol abuse	34/64 (53%)
Stimulant abuse	25/64 (39%)
Hypertension	8/67 (12%)
Type 2 diabetes	7/67 (10%)
Hyperlipidemia	6/67 (9%)
Hepatitis C infection	18/67 (27%)
End stage liver disease	3/67 (4%)
Chronic renal disease	6/67 (9%)
Chronic obstructive pulmonary disease	3/67 (4%)
Cerebrovascular disease	2/67 (3%)
Non-AIDS defining cancer	9/67 (13%)
Lipodystrophy	4/67 (6%)
Smoking ever	13/67 (19%)

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Table 2

Viral and biologic characteristics of the sample.

HIV-related characteristics	
HIV infection duration (mean) (SD, range, n)	20.7 years (7.9, 3–36, 72)
Nadir CD4+ T-cell count (median) (IQR, range, n)	32 cells/mm3 (107, 0-491, 73)
Antemortem blood viral load (median) (IQR, range, n)[a]	16700 copies/mL (19700, 40-750000, 53)
Antemortem CD4+ T-cell count (median) (IQR, range, n)	53 cells/mm3 (190, 0–577, 66)
CD4+ T-cell measurement interval (median) (IQR, range, n)	23 months (13, 5–87, 39)
HAND: impaired	56/74 (76%)
Histological characteristics	
HIVE	2/74 (3%)
CMV infection	1/74 (1%)
Cryptococcosis	3/74 (4%)
Biomarkers	
Plasma sCD163 (mean) (SD, range, n)	1160 ng/mL (691, 333–3685, 54)
Plasma sCD163 measurement interval (median) (IQR, range, n)	5 months (6, 0–18, 54)
CSF sCD163 (mean) (SD, range, n)	44 ng/mL (16, 27–111, 32)
CSF sCD163 measurement interval (median) (IQR, range, n)	6 months (11, 1–31, 32)

[a]Blood HIV viral load were drawn within 12 months of the date of death.

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Table 3

Multivariable regression results for plasma sCD163.

	Coefficient	95% CI	*p* value	Model *p* value	*p*-value after FDR	Covariates[a]
MAP2, dorsolateral frontal cortex	−0.23	−0.41, −0.06	0.007	0.03	0.04	Ethnicity
MAP2, putamen	−0.32	−0.52, −0.12	0.004	<0.001	0.02	Gender, COPD, lipodystrophy
MAP2, hippocampus	−0.23	−0.35, −0.10	0.001	0.003	0.01	Gender, COPD, lipodystrophy, NADC
SYP, putamen	−0.23	−0.42, −0.03	0.02	0.008	0.09	Gender, diabetes, cryptococcosis
SYP, hippocampus	−0.25	−0.39, −0.10	0.003	0.01	0.02	Gender, alcohol abuse, stimulant abuse, lipodystrophy
HLA-DR, composite	0.11	0.05, 0.17	<0.001	0.02	0.01	Gender, NADC, lipodystrophy, age, alcohol abuse, stimulant abuse
HLA-DR, putamen	0.17	0.08, 0.26	<0.001	0.001	0.008	ESLD, smoking ever

[a]plasma sCD163 measurement interval was included in all models

COPD: chronic obstructive pulmonary disease

NADC: non-AIDS defining cancer

ESLD: end-stage liver disease

FDR: false discovery rate