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Increasing Neuroinflammation relates to Increasing Neurodegeneration in PWH

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CHARTER
CNS HIV Anti-Retroviral Therapy Effects Research
CNS HIV ANTI-RETROVIRAL THERAPY EFFECTS RESEARCH

Objective

Evaluate the hypothesis that increases in biomarkers of neuroinflammation will be correlated with increases in levels of neurodegeneration biomarkers at follow up

Background & Significance

- Neurodegenerative disorders are arising more frequently among people with HIV (PWH) as they age on successful antiretroviral therapy (ART)
- Both aging and HIV infection are associated with inflammation and elevations in markers of neuronal injury

Specific Aims

We determined the association of Cerebrospinal fluid (CSF) and plasma inflammatory biomarkers with neurodegeneration biomarkers in PWH after ART.

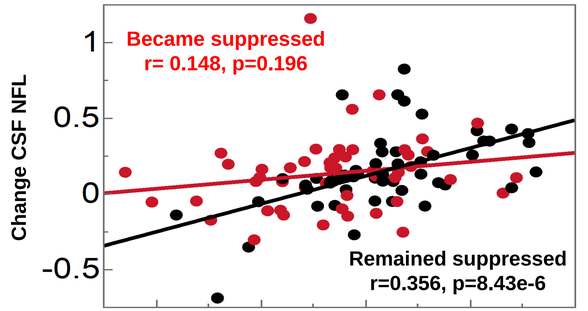
Method

- PWH in the US multisite CHARTER Aging project were assessed at a baseline visit and again after 12 years using standardized evaluations
- All participants had plasma HIV RNA ≤50 copies/ml at follow-up
- Participants with severely confounding medical and neuropsychiatric conditions such as renal failure on dialysis or active psychosis were excluded.
- A panel of 14 soluble biomarkers measured in plasma and CSF by immunoassay at both assessments (sCD40L, IL-6, sTNFR-II, CRP, Neopterin, MCP-1, sCD14, d-dimer, NFL, total Tau, phosphorylated tau, Ab42, sAPPalpha, 8-oxo-DG).
- Factor analyses to reduce biomarker dimensionality
- Pearson correlations for tested associations between change in inflammation and neurodegeneration

Table 1. Changes in plasma biomarkers (mean+/-SD) comparing PWH who remained suppressed to those who became suppressed

Biomarker	All participants	Remained suppressed	Became suppressed	P-value
Interleukin 6 (IL-6)	0.0849+/-0.423	0.124+/-0.0570	0.441+/-0.0581	0.0395
CD40L	0.0952+/-0.827	0.145+/-0.767	0.0423+/-0.0890	0.237
sTNFRII(soluble tumor necrosis factor receptor)	-0.0245+/-0.260	-0.007+/-0.244	-0.0425+/-0.276	0.584
CRP(C reactive protein)	0.129+/-0.622	0.182+/-0.643	0.075+/-0.601	0.653
Neopterin	-0.0452+/-0.206	0.033+/-0.206	-0.127+/-0.173	<0.0001
MCP-1(Monocyte chemoattractant protein)	-0.0185+/-0.189	-0.0132+/-0.174	-0.240+/-0.281	0.858
Aβ42(Amyloid β)	-0.090+/-0.456	0.062+/-0.424	0.118+/-0.490	0.077
sAPP(Alzheimer precursor protein)	0.0122+/-0.498	0.054+/-0.464	-0.082+/-0.527	0.122
D-dimer	0.151+/-0.260	0.193+/-0.247	0.108+/-0.268	0.153
8-oxo-DG(7,8 dihydro 8 oxo guanine)	0.116+/-0.353	0.115+/-0.280	0.118+/-0.417	0.247
sCD14	-0.038+/-0.780	-0.0292+/-0.876	-0.046+/-0.675	0.902

Increases in biomarkers of inflammation in CSF were associated with increases in a marker of neuronal injury, specifically in PWH who remained virally suppressed during follow-up



Results

- Participants were 108 ART-treated PWH, all virally suppressed at follow-up, mean (SD) baseline age years 56 +/-8, 15(14.15%) female, 91 (85.84%) male, 54 (50.95%) non-white, and median (IQR) current CD4+ T-cells 576 (368, 860), CD4+ nadir 96 (21, 200).
- The neurodegeneration factor analysis yielded 2 Factors: Factor 1 loading on Amyloid β 1-42 (Aβ42) and Factor 2 loading on neurofilament-light (NFL).
- The CSF immune factor analysis yielded 2 Factors with Factor 1 loading on sTNFRII and neopterin and Factor 2 loading on MCP-1 and sCD14.
- The plasma immune factor analysis yielded 2 factors: Factor 1 loading on CRP and d-dimer, Factor 2 loading on MCP1 and sCD14

Results, Continue

- In a multivariable model predicting CSF NFL (CSF Neuro Factor2) from viral suppression and CSF Immune Factor1, the interaction showed a trend towards significance (p=0.0508); the main effect of CSF Immune Factor1 was significant (r=0.356, p=8.43e-6, Bonferroni corrected p=6.75e-5), while viral suppression was not (p=0.202)
- Higher neuroinflammation Factor 1 (loading on change in CSF sTNFRII and neopterin) correlated with higher neurodegeneration Factor 2 for those who remained suppressed, but not for those who became suppressed over follow-up.
- CSF immune Factor1 was lower at baseline in those who became suppressed (mean +/- SD -0.304 +/- 0.790), but increased slightly in those who remained suppressed (0.175 +/- 0.743, p=0.0026).
- Factor1 was not related to any of the other neurodegeneration biomarkers (tTau, pTau, Ab42, sAPP, 8-oxo-DG).
- The plasma immune Factor1 loading on CRP and d-dimer correlated with neurodegenerative Factor 2 loading on NFL (p=0.0327).
- Increasing age correlated with increases in CSF NFL (p<0.0001). Sex and ethnicity did not significantly influence any of the CSF immune or CSF neuro factors. In a multivariable model, CSF immune Factor1 remained significant (p=0.0002), but age did not (p=0.605).

Conclusions

increases in inflammation were linked to increases in neurodegeneration in virally suppressed PWH, suggesting that interventions such as anti-inflammatory medications (eg. TNF-α inhibitors) might prevent neurodegeneration.

Table 2. Changes in CSF biomarkers (mean+/-SD) comparing PWH who remained suppressed to those who became suppressed

Biomarker	All participants	Remained suppressed	Became suppressed	P-value
Il-6	0.020+/-0.253	0.057+/-0.266	-0.0184+/-0.236	0.097
NFL(Neurofilament light)	0.131+/-0.261	0.146+/-0.256	0.116+/-0.269	0.598
sTNFRII	0.0503+/-0.124	0.076+/-0.095	0.0239+/-0.0143	0.0024
Total Tau	0.0834+/-0.254	0.061+/-0.253	0.0108+/-0.256	0.437
Neopterin	-0.0146+/-0.236	0.037+/-0.156	-0.070+/-0.291	0.0026
MCP-1	-0.090+/-0.341	-0.0114+/-0.174	-0.0690+/-0.123	0.563
Aβ42	0.0435+/-0.221	0.440+/-0.180	0.043+/-0.260	0.441
sAPP	-0.770+/-0.143	-0.734+/-0.304	-0.651+/-0.0188	0.953
Phosphorylated tau	0.0266+/-0.108	0.0212+/-0.066	0.0322+/-0.0140	0.328
8-oxo-DG	-0.048+/-0.220	-0.020+/-0.230	-0.078+/-0.206	0.210
sCD14	0.078+/-0.574	0.046+/-0.715	0.011+/-0.380	0.250

NNTC/CHARTER NEUROAIDS DATA RESOURCE WWW.NNTC.ORG

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