Poster 00408

High Protein Carbonyl Levels Correlate with Abnormal White Matter in People with HIV

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BACKGROUND

- Structural abnormalities, including white matter (WM) abnormalities are more common in people with HIV (PWH) than in people without HIV (PWOH) but the underlying mechanisms are not known.
- WM abnormalities have been shown to correlate with neurocognitive impairment and neuropsychiatric disorders in both PWH and PWOH
- Increased levels of oxidative stress are associated with many conditions including HIV on suppressive ART, neurodegenerative and psychiatric disorders.
- Protein oxidation, measured by protein carbonyl concentration, reflects cumulative exposure to oxidative stress.
- **Objective: To determine relationships between biomarkers of oxidative stress, inflammation and neurodegeneration in blood and CSF and structural abnormalities on magnetic resonance imaging (MRI) in PWH**

METHODS

- Participants and study design. Cross-sectional analysis of subgroup of the CHARTER Aging study (a U.S. multisite cohort study of PWH). We compared concentrations of soluble blood and cerebrospinal fluid (CSF) biomarkers to findings from structural brain MRI in the subset of participants with both imaging and biomarker data.
- Imaging. A semi-automated multi-channel segmentation approach estimated the volume of abnormal WM normalized for total WM volume. Total gray matter (GM) volume was normalized for intracranial volume.
- Biomarkers. 15 soluble biomarkers were measured in blood and/or CSF by commercial immunoassay. Blood and CSF: protein carbonyls (PCs), 8-OH deoxyguanosine (8-OH-dG), IL-6, MCP-1, sCD14, sTNFR-II, Neopterin, Aβ-42, sAPPα, Blood only: CRP, d-dimer, sCD40L. CSF only: NFL, total Tau, Tau pT181
- Statistical Analysis. Correlations and multivariable linear regression models were conducted to examine associations between biomarkers and imaging findings. All imaging analysis were adjusted for scanner. Covariates included in the regressions included scanner, demographics, HIV disease characteristics and comorbidities (eg diabetes, HCV).

- Greater protein oxidation, as indexed by plasma protein carbonyls, is associated with more white matter abnormalities among PWH.
- Protein carbonyls in blood may be a valuable biomarker of oxidative stress and its associated adverse health effects, including within the central nervous system.

Figures: Correlations and regression lines with 95% confidence intervals for comparisons between biomarkers and MRI findings. Higher plasma PCs correlated significantly with higher proportion of abnormal white matter (left). Higher CSF NFL and CSF total Tau were associated with lower gray matter volume (middle, right panels).

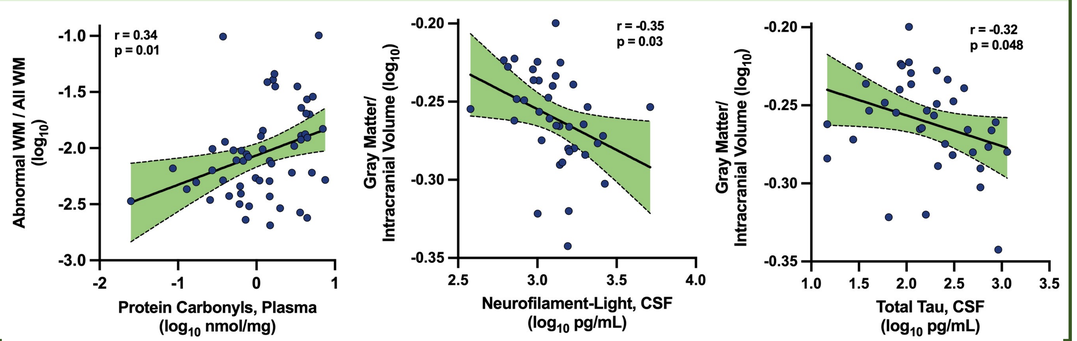

Table: Regression table for analysis of proportion of white matter abnormalities. Univariable analyses are all adjusted by scanner. Best multivariable model was determined using the Akaike information criterion and backward selection.

	Univariable		Multivariable		Risk Direction
	β	p	β	p	
Plasma PCs	0.27	0.005	0.188	0.030	Higher
Sex	0.350	0.022	0.242	0.062	Women
Race/Ethnicity	0.16	0.028	0.116	0.005	Black
HCV	0.128	0.030	-	-	Seropositive
Age	0.015	0.054	0.020	0.005	Older
Nadir CD4	2.9E-04	0.498	-	-	-
ART Use	0.064	0.588	-	-	-
Current CD4	-7.2E-05	0.658	-	-	-
AIDS Diagnosis	0.010	0.905	-	-	-
HIV RNA ≤ 200	-0.002	0.978	-	-	-

RESULTS

- Participant characteristics. 55 participants had both plasma biomarker and MRI data. Mean age was 56.9 years, 86.8% were men, 52.8% were either black or Hispanic, 96.2% were on ART, plasma HIV RNA <50 copies/mL in 81.6%, and median CD4+ count was 543/μL. 54% of the sample were HCV seropositive and 20% had diabetes. 35 (64%) also had CSF biomarker data.
- Biomarker and MRI findings analyses. Higher plasma PCs correlated with higher proportion of abnormal WM volume (p=0.011, r=0.34). Higher CSF neurofilament-light (NFL, p=0.029, r=-0.35) and CSF total Tau (p=0.048, r=-0.32) were associated with lower GM volume. In multivariable linear regression models, only plasma PCs remained associated with higher proportion of abnormal WM. When analysis repeated with only participants on suppressive ART, all associations with PCs remained significant.

CONCLUSIONS

- Protein oxidation, which has been linked to risk for Alzheimer's Disease and to conditions causing cerebral small vessel disease such as diabetes, is associated with proportionately more abnormal WM, which has been associated with cognitive impairment in PWH.
- Out of a panel of indicators of inflammation, neurodegeneration and oxidative stress, only plasma protein carbonyl levels correlate significantly with abnormal white matter. As oxidative stress results from multiple distinct processes, protein carbonyls may be an aggregate measure of physiologic stressors (eg inflammation, ischemia, hyperglycemia/toxic metabolic).
- If larger projects validate this finding, the results would support the hypothesis that treating with antioxidants could potentially treat or prevent WM injury and potentially improve cognition and daily functioning in PWH.

ACKNOWLEDGEMENTS

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