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Nucleic Acid Oxidation is Associated With Biomarkers of Neurodegeneration In CSF Among People with HIV Taking Suppressive Antiretroviral Therapy

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CNS HIV AntiRetroviral Therapy Effects Research (CHARTER)

Objective

Evaluate the relationship between nucleic acid oxidation and neurodegeneration in people with HIV (PWH)

Background & Significance

- Oxidative stress is common in HIV, even among virologically suppressed PWH
- Alzheimer's Disease (AD) changes including elevated Tau and reduced Aβ may be common in PWH
- HIV and AD are both associated with oxidative stress
- HIV proteins and ARVs can damage mitochondria, which can generate reactive oxygen species (ROS)
- Proteolytic processing of the amyloid precursor protein (APP) via amyloidogenic pathways yields neurotoxic and oxidative stress-producing Aβ-42 peptide
- Oxidative stress-induced DNA damage is indexed by a marker of oxidatively damaged guanine, increased 7,8-dihydro-8-oxoguanine (8-oxo-dG) levels.
- Increased 8-oxo-dG in nuclear DNA is accompanied by a decrease in mitochondrial DNA content in frontal cortex

Hypothesis

Oxidative stress affecting DNA will be associated with biomarkers of neurodegeneration in CSF in PWH

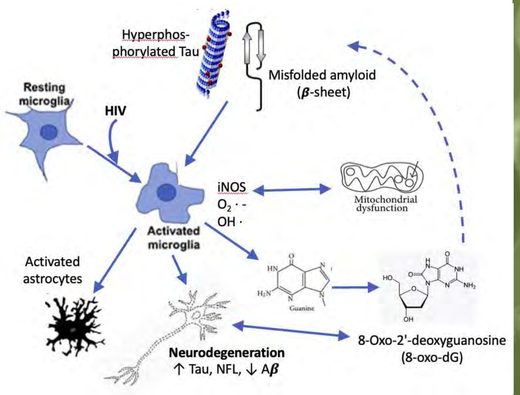
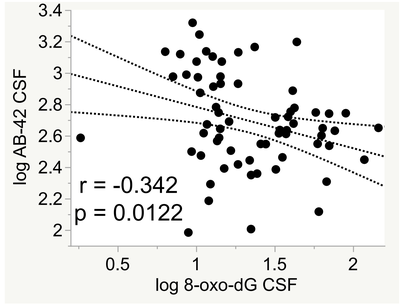
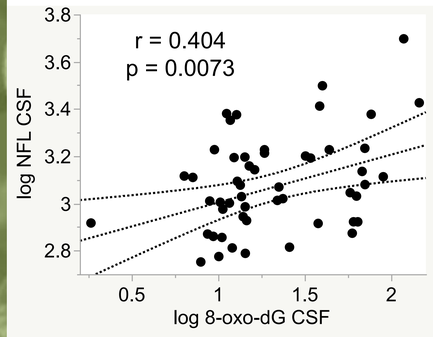


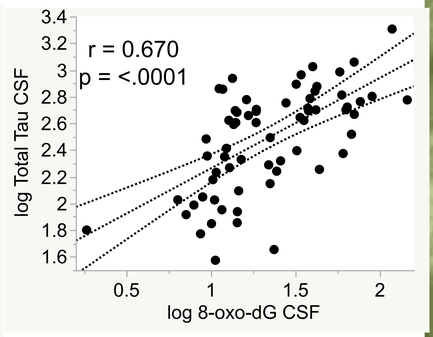
Figure 1. Conceptual Model: Despite viral suppression, mitochondrial dysfunction occurs in HIV. Microglia are activated by HIV and abnormal proteins, leading to oxidation of nucleic acids and neurodegeneration indexed by CSF NFL, Tau and Aβ.

Results

Figure 2. Higher CSF levels of 8-oxo-dG correlate with reduced Aβ-42 and increased NFL and Total Tau







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Methods

- CNS HIV Antiretroviral Effects Research (CHARTER) Aging study participants
- Inclusions: HIV+ with plasma HIV RNA ≤50 copies/ml
- Exclusions: significant CNS confounding conditions
- Phlebotomy and lumbar pucture
- Total Tau and Aβ-42 measured by bead suspension array
- NFL and 8-oxo-dG using ELISA
- Blood CD4+ T-cell counts measured in a CLIA-certified laboratory
- HIV RNA levels by real time PCR (LLQ 50 copies/mL)

Additional Results

- Men had higher CSF NFL (p = 0.049) and Aβ-42 (p = 0.042) than women
- Hispanics had higher Aβ-42 than blacks (p=0.021) and whites (p = 0.16)
- Increasing age was associated with higher total Tau and NFL levels
- Relationships of 8-oxo-dG levels to NFL, total Tau and Aβ-42 remained after adjusting for age, sex and ethnicity.
- 8-oxo-dG levels were not related to age, sex or ethnicity.
- 8-oxo-dG in plasma not related to neurodegeneration biomarkers
- NP global and domain performance were not related to any of the biomarkers

Conclusions

- Nucleic acid oxidation associated with worse CSF biomarkers of neurodegeneration reflecting AD and axonal damage in virally suppressed PWH
- Specificity of association for CSF, but not plasma 8-oxo-dG suggests oxidative stress more important in CNS
- Potential sources of oxidative stress: low-level HIV replication, inflammation, mitochondrial dysfunction and specific ART drugs
- Oxidative stress in HIV may play a role in neurodegeneration, or neurodegeneration may provoke oxidative stress
- Absence of links to neurocognitive impairment might be explained by the occurrence of these alterations before the onset of neurocognitive impairment

Table. Demographics and clinical characteristics

Age, years (mean+/-SD)	55.0 (9.3)
Education	13.1 (2.3)
Female sex (N, %)	10 (18.9%)
non-Hispanic white race/ethnicity (N, %)	25 (48.1%)
CD4 nadir (median, IQR)	115 (28, 196)
Current CD4 (median, IQR)	568 (311, 751)
History of d-drug exposure (N, %)	33 (62.3%)

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