Mitochondrial DNA Is Associated With Inflammation and Neurocognitive Deficits in HIV Infection
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Background: HIV enters the central nervous system (CNS) early in infection leading to persistent inflammation and often resulting in HIV associated neurocognitive disorders (HAND). Cells in the CSF tend to be activated and inflammatory factors may increase cell death, releasing mitochondrial DNA (mtDNA) into the cerebrospinal fluid (CSF). MtDNA itself can induce a potent inflammatory response and may contribute to the persistent inflammation in the CNS. We hypothesized that higher levels of free mtDNA in CSF would be associated with higher levels of immune activation, pro-inflammatory cytokines, and chemokines, as well as with worse neurocognitive performance.

Methodology: We performed a retrospective evaluation of CSF supernatant samples collected from 31 HIV infected individuals enrolled in an NIMH-funded cohort, 16 of whom had available longitudinal assessments. Neurocognitive performance, summarized by the global deficit score (GDS), sociodemographic and clinical data were collected for each participant. Neurocognitive impairment (NCI) was defined as a GDS ≥ 0.5. We quantified mtDNA load (ML) in CSF using the highly sensitive droplet digital PCR platform. Biomarkers of immune activation (sCD14 and sCD163), pro-inflammatory cytokines (TNF-α, IL-6), and chemokines (MCP-1, IP-10) were measured using immunoassays. Statistical analyses were performed using R software.

Results: Using mixed effects regression analysis and all samples available, a higher ML in CSF was associated with greater neurocognitive dysfunction (GDS, p=0.002), higher levels of the CNS inflammatory chemokine IP-10 (p=0.03) and sCD14 (p=0.01). In cross-sectional analysis, the association of ML with CNS inflammation was more prominent in the subgroup of patients with a detectable CSF HIV VL (IP-10, r=0.7, p=0.001), and the subgroup of patient with a CD4 count <350 (IP-10, r=0.68, p=0.03). In this latter subset, ML also correlated with CD4 nadir (r=0.71, p=0.03). When NCI was present, a higher ML in CSF correlated with greater neurocognitive dysfunction (GDS, r=0.78, p=0.001), increased CNS levels of the inflammatory chemokine IP-10 (r=0.7, p=0.001), and increased plasma levels of the inflammatory chemokine MCP-1 (r=0.67, p=0.01). However, there was no association between CSF VL and GDS, and IP-10 was only weakly associated with GDS (r=0.53, p=0.06).

Conclusions: Extracellular mtDNA may represent a novel biomarker of neurologic damage that not only is easily measurable in CSF, but also may associate better with neurocognitive dysfunction than other biomarkers. Additionally, mtDNA may contribute to persistent inflammation of the CNS seen in HIV infection. A better understanding the role of mtDNA in the CNS inflammation could lead to improved therapies for HAND.