On Cerebrospinal Fluid Biomarkers of HIV-1 Infection

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I. Gisslén M, Krut J, Andreasson U, Blennow K, Cinque P, Brew BJ, Spudich S, Hagberg L, Rosengren L, Price RW, Zetterberg H. **Amyloid and tau cerebrospinal fluid biomarkers in HIV infection**. BMC Neurology. 2009; 9:63.

II. Krut JJ, Zetterberg H, Blennow K, Cinque P, Hagberg L, Price RW, Studahl M, Gisslén M. **Cerebrospinal fluid Alzheimer's biomarker profiles in CNS infections**. J Neur. 2013; 260:620-626.

III. Krut JJ, Mellberg T, Price RW, Hagberg L, Fuchs D, Rosengren L, Nilsson S, Zetterberg H, Gisslén M. **Biomarker Evidence of Axonal Injury in Neuroasymptomatic HIV-1 Patients**. PLoS One. 2014 Feb 11;9(2):e88591

IV. Krut JJ, Price RW, Zetterberg H, Fuchs D, Hagberg L, Yilmaz A, Cinque P, Nilsson S, Gisslén M. **No support for premature CNS aging in HIV-1 when measured by cerebrospinal fluid hyperphosphorylated tau (p-tau)**. In submission

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ABSTRACT

HIV invades the central nervous system (CNS) shortly after transmission and is present throughout the course of infection, causing immune activation and neuroinflammation. If left untreated, more than 20% of patients with late-stage HIV/AIDS develop HIV-associated dementia (HAD). With combined antiretroviral treatment (cART), HAD is rare, but mild neurocognitive deficits are commonly noted, summarized in the concept of HIV-associated neurocognitive disorders (HAND). The diagnosis of HAND relies solely on neuropsychological testing, which might overestimate the prevalence of HAND. Analysis of biomarkers could enhance diagnostic precision. With an aging HIV-infected population, methods to distinguish HAND from other dementias, mainly Alzheimer's disease (AD), will be important.

This thesis evaluates biomarkers related to: neuronal injury (neurofilament light chain protein (NFL) and total tau (t-tau)); immune activation (neopterin); and altered metabolism (soluble amyloid precursor protein α and -β (sAPP), beta-amyloid$_{1\text{-}42}$ (A$\beta_{1\text{-}42}$) and phosphorylated tau (p-tau)) in cerebrospinal fluid (CSF) of HIV patients with and without cognitive deficits. For purposes of differential diagnosis, AD patients and HIV-negative subjects with CNS infections were included.

HAD-patients exhibited a biomarker pattern with normal to low A$\beta_{1\text{-}42}$, decreased sAPPs, normal p-tau and increased t-tau, differentiating HAD from AD, neuroasymptomatic (NA) HIV-infected patients, and controls. Although CSF p-tau occurs physiologically with aging, p-tau levels were normal or decreased in HIV. HIV-related opportunistic infections and CNS-infections in HIV-negatives were similar to HAD, indicating that neuroinflammation might induce a pathologic processing of amyloid, separate from the metabolism in AD. Amyloid and tau metabolites could be useful biomarkers to distinguish HAD from AD.

CSF NFL was highest in the HAD patients, but NA patients, both with and without cART, also exhibited increases of NFL. This indicates ongoing axonal disruption at all stages of HIV, also in some patients on cART. Likely this is due to HIV-induced axonal disruption. CSF NFL is increased at earlier ages in HIV-infected patients as compared to controls, corresponding to 18.5 years in untreated NA and 3.9 years in NA with cART.

Keywords: HIV-associated neurocognitive disorders, HIV-1, amyloid protein, tau protein, neurofilament protein, biomarker, central nervous system, cerebrospinal fluid.

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