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Plasma cytokine concentrations associated with HIV/hepatitis C coinfection are related to attention, executive and psychomotor functioning

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ABSTRACT

Cytokine disturbances have been linked to brain dysfunction among HIV-infected people. Past studies have not simultaneously examined a large set of cytokine measures and their relationships to HIV-associated neurocognitive deficits. We hypothesized that performance on measures of attention and executive and psychomotor functions would be associated with plasma cytokine concentrations in HIV-infected individuals. Plasma samples drawn from 30 HIV-infected and 37 HIV seronegative individuals were analyzed via xMAP multiplexed bead array immunoassay to determine concentrations of 13 cytokines. Performance on Trail Making A/B, Stroop Test, Letter–Number Sequencing, Digit Symbol Coding, Symbol Search, and Grooved Pegboard tests was assessed. Statistical analyses were performed to examine group differences in cytokine concentrations, and associations between cytokine and HIV clinical variables and neurocognitive performance. Significant HIV effects were found on 7 of the 13 cytokines, primarily with respect to interleukins. HIV clinical factors (CD4 and HIV RNA levels, duration of illness, antiretroviral treatment) and hepatitis C status were associated with specific plasma cytokine concentrations. Neurocognitive measures were associated with cytokine concentrations, most consistently among the interleukins and IP-10. Generally, cytokine concentrations were among the strongest predictors of neurocognitive function relative to other clinical factors, which reinforces their potential importance in examining the neuropathological processes of HIV. The findings also point to the potential value of simultaneously examining a panel of biomarkers. The current results suggest that a complex relationship likely exists among cytokines [how?] and that these relationships are mediated not only by HIV infection but also by antiretroviral treatment and other comorbid conditions.

1. Introduction

HIV-associated neurocognitive and behavioral disturbances are well recognized and continue to occur despite widespread use of highly active antiretroviral therapies (HAART), which can very effectively reduce HIV RNA level and enhances the host immune status. HIV crosses the blood brain barrier and enters the brain very soon after initial infection and replicates in perivascular macrophages and microglia (Budka, 1991). In this regard, HIV infection triggers inflammatory responses associated with microglial cell activation and attendant release of neurotoxic pro-inflammatory cytokines (Gonzalez-Scarano and Martin-Garcia, 2005; Gisolf et al., 2000; Rostasy et al., 2000). The inflammatory component of HIV infection in the central nervous system (CNS) is regarded as a critical component of HIV-associated brain dysfunction (Merrill and Chen, 1991; Cartier et al., 2005; Minagar et al., 2002; Gorg et al., 2006; Guyon et al., 2008; Lewis et al., 2008), with its severity strongly correlating with the abundance of activated monocytes in the brain (Langford and Masliah, 2001). HIV-associated neuronal loss and dysfunction are mediated by increased apoptosis and axonal degeneration throughout the brain (Chiodi, 2006; Sabri et al., 2003; Gray et al., 1996). Frontal-striatal areas have been implicated (Ernst and Chang, 2004; Cloak et al., 2004; Chang et al., 2008; Thompson et al., 2001, 2003; Filippi et al., 2001), consistent with findings of attention-executive and psychomotor impairments common in HIV-infected persons. Neuroimaging approaches, such as magnetic resonance spectroscopy (MRS), can detect abnormalities that reflect cerebral inflammation in HIV-infected people (Chang et al., 2004; Paul et al., 2007, 2008). Previous MRS studies in HIV have shown abnormal cerebral metabolites preferentially in the

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