CSF biomarkers in HIV dementia

Through a glass darkly

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A reliable biomarker for HIV-associated dementia (HIV-D) has eluded neuro-AIDS investigators for more than 2 decades. An urgent need remains, because although the incidence of HIV-D has declined among patients treated with highly active antiretroviral therapy, prevalence has increased, and a more insidious cognitive decline, minor cognitive motor disorder (MC/MD), has become common.1,2

Efforts to diagnose, evaluate treatments, and identify risk factors are held back by lack of disease-specific biomarkers. Routine radiographic findings of “HIV encephalitis” do not correlate strongly with cognitive dysfunction, and although advanced imaging modalities such as magnetic resonance spectroscopy (MRS), magnetization transfer imaging, and diffusion tensor imaging show promising, sometimes striking, correlations, these modalities will likely remain impractical in most settings where costs are prohibitive and interpretive expertise is limited.3-5

An ideal biomarker for HIV-associated brain disease would be objective, quantitative, and scalable for wide use. Operationally, it would serve 1) diagnosis of HIV-D and MC/MD, 2) identification of patients at risk, 3) detection of disease progression, 4) confirmation of arrested or static encephalopathy, and 5) measurement of treatment response. A single biomarker sufficient for all these aims is implausible; rather, complementary markers likely will be required.

Moving from bedside to bench, biomarkers ideally should further the science of neuro-AIDS by means of transparent associations with HIV neuropathogenesis. Numerous viral and host factors have been implicated; how these elements interact and converge to produce the particular patterns of HIV-associated brain injury remains unclear. The most attractive grand narrative is also the oldest, namely, that brain injury in HIV is driven by immunopathology. Monocyte-derived macrophages (MDMs) traffic between blood and brain early in infection, carry virus into the CNS, activate other immune cells, amplify inflammation, and secrete potent neurotoxins.6

In the battle with HIV, neuronal tissue injury and cell death are a consequence of immunologic “friendly fire.”

Neuro-AIDS investigators have focused largely on the CSF as a source of biomarkers in the belief that this compartment represents a window onto the brain microenvironment. CSF macromolecular analysis has led to reasonably sensitive and specific biomarkers for dementia of the Alzheimer type (DAT).7 Progress, however, was directed by pathognomonic brain lesions: the senile plaques of filamentous β-amyloid, and neurofibrillary tangles of hyperphosphorylated tau protein. Unfortunately, the HIV-diseased brain has not been so cooperative. No lesions reliably distinguish patients with clinical dementia from those with preserved cognitive function.8 Biomarker research has relied on identifying signature molecules of brain injury pathways familiar from other diseases, e.g., stroke, epilepsy, Alzheimer disease (AD), Parkinson disease. Hence, it is not surprising that proposed neuro-AIDS disease mechanisms, such as oxidative stress, neuroinflammation, and excitotoxicity, are common to many brain diseases. It is also not surprising that unique or diseasespecific biomarkers remain elusive.

Two studies reported in this issue of Neurology® illustrate uses of CSF biomarkers in HIV-infected patients with cognitive impairment. Schifitto et al.9 investigate treatment effect of selegiline, a drug with antioxidant properties, on CSF protein carbonyls, markers of oxidative stress. Clifford et al.10 compare AD biomarkers in cognitively impaired HIV-infected patients, controls, and patients with mild DAT.

Schifitto et al. summarize data from a substudy of seropositive subjects with cognitive impairment who participated in a 24-week trial of selegiline, 3 or 6 mg/d, vs placebo. As previously reported, no benefit of selegiline was seen on cognitive outcomes or functional measures.11 Of 128 subjects enrolled, 62 underwent MRS at baseline and weeks 12 and 24, whereas 47 subjects provided CSF samples at base-
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CSF.12 Low levels of tau and P-tau181 distinguished subjects with HIV-associated cognitive impairment (CI) from those with preserved cognition (NC) and controls. Sensitivity and specificity in this relatively small (n = 31) sample were 100% and 75%, respectively. In a later study, the same group performed similar proteomic analysis on CSF samples from subjects with CI and NC from the same cohort. Several proteins involved in cell signaling, phagocytosis, and cell-matrix interactions were identified from pooled samples that distinguished the CI group from the NC group. Unfortunately, low CSF protein concentrations and sample volumes limit comparison of individual samples at this time. In fact, regardless of compartment, daunting technical challenges remain for proteomics and other high-content “-omics,” e.g., lipidomics, transcriptomics, metabolomics, that are applicable to neuro-AIDS research. These approaches nevertheless offer new insights into virus-host interactions and may consequently open new windows into the neuropathogenesis of HIV. Early results raise hope that disease-specific biomarkers will emerge to meet the pressing needs of clinicians and afflicted patients.

DISCLOSURE
Dr. McGuire serves on clinical advisory boards of Opexa Therapeutics and Atrielle ImmunoTherapeutics, Inc.; is a member of the CNS and Cardiovascular Events Committee of Affymax, Inc.; is a member of the advisory council of the Gill Heart Institute, and Chief Medical Officer of Acologix, Inc.; serves as a Director of Rio Pharmaceuticals; has served as a consultant for Seattle Genetics, GangaGen, Inc., and Geron Corporation; and has received travel funds and honoraria from the NINDS.

REFERENCES


