Biomarkers of HIV Associated Neurocognitive Disorders

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EDITORIAL

Of the 35.3 million people infected with the human immunodeficiency virus (HIV) worldwide, reported by the United Nations in 2012, about 40–60% of the individuals will eventually develop neurocognitive disorders that can be attributed to the presence of HIV-1 in the central nervous system (CNS) and its associated neurotoxins and neuroinflammation. Accordingly, identification of the biomarkers associated with HIV-associated Neurocognitive Disorders (HAND) is important to understand the biology of these disorders, developing effective therapies, and evaluating therapeutic outcomes. However, recently a ray of hope has emerged, due to sustained efforts in the introduction of antiretroviral therapy and preventive measures resulting into the global decline of the incidence.

There were 2.3 (1.9–2.7) million new HIV infections globally, showing a 33% decline in the number of new infections from 3.4 (3.1–3.7) million in 2001. At the same time the number of AIDS deaths is also declining with 1.6 (1.4–1.9) million AIDS deaths in 2012, down from 2.3 (2.1–2.6) million in 2005. HIV-1 enters the brain shortly after infection, which may lead to neurological complications ranging from very mild cognitive impairment to encephalitis and severe dementia. The HAND is characterized by development of cognitive, behavioral and motor abnormalities, and occurs in approximately 50% of HIV infected individuals [1]. Although HAND is diagnosed based on the neurological/psychiatric tests, they are not precise. Blood Brain Barrier (BBB) is a tight protective barrier which prevents the entry of molecules and infectious agents into the brain from the blood stream. At the same time because of this impermeability to the most of the molecules, delivery of therapeutic/diagnostic molecules into the brain across the BBB makes almost impossible.

A biomarker is a “characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic response to a therapeutic intervention”. Biomarkers of systemic infection activity in HIV, used clinically for monitoring the disease in resource-rich settings, are CD4 T-lymphocyte count and viral load (HIV-RNA). Although many potential biomarkers have been proposed, there is lack of sensitive and highly specific markers of HAND progression [2,3]. Although blood is easier to obtain than CSF, CD4 count and viral load can only be an approximate guide to probability of HAND.

And also in the post-CART era, HAND is increasingly identified in patients with high CD4 counts and undetectable blood viral loads. CD4 cell count below 200/µL at least in the pre-CART era was a useful indicator for the risk of HAND [4]. Increased levels of sCD40L and TNF-α in cerebrospinal fluid (CSF) and plasma have been reported as a marker for HAND [5].

HAND was reported to be associated with pathological changes in the brain that include generalized atrophy, changes in white matter causing leukoencephalopathy, microglial nodules typical of viral encephalitis, and multinucleated giant cells that seem to be infected directly by HIV on antigen staining [6]. In untreated infection, severity of dementia was more closely associated with inflammatory response markers than with viral load, although CSF viral load was modestly associated with clinical manifestations [7].

CSF Beta-2-microglobulin (a marker of cytotoxic T-lymphocytes in the CNS) concentrations correlate with the risk of HAND in patients with advanced HIV [8]. One of the more promising areas for potential peripheral biomarkers has been monitoring of monocyte activation. CD14+/CD69+ monocytes particularly the CD14lo/CD69hi subset in peripheral blood appears to be important in HAND pathogenesis, although they may be nonspecifically elevated in a range of infections [9]. Detection of HIV DNA circulating within mononuclear cells could also identify a raised risk for HIV-associated neurocognitive disorder [10]. Another measure of activated monocytes seems to be soluble CD163—a scavenger receptor that is up regulated in activated monocytes [11]. Recent studies suggest that this receptor might remain raised in patients with HIV-associated neurocognitive disorder.

The clinical usefulness of inflammatory markers in the CSF has been low, but these measures could potentially identify patients at risk of HIV-associated neurocognitive disorder. In patients with advanced HIV disease, elevated levels of CSF neopterin (marker for monocytes, macrophages, microglia, and astrocytes) IgG index associated with increased risk of dementia [12]. Quinolinic acid (QUIN) is a product of the kynurenine pathway for tryptophan metabolism produced by monocytes in response to interferons, especially interferon γ (IFN-γ) and HIV proteins among other agents. Increased CSF QUIN production
may be seen in opportunistic infections and HIV dementia; in the latter concentrations correlate with dementia severity [13]. S-100 is an acidic calcium binding protein found in astrocytes, exists in dimers containing α and/or β subunits. Raised S100β is associated with increased severity of HAND and more rapid progression to dementia [14]. Neurofilament light chain (NFL) is a major structural protein of neurons. NFL is significantly raised in HAND and reported as a preclinical indicator of risk of HAND [15].

Amyloid precursor protein (APP) is an integral membrane protein expressed in many tissues and concentrated in the synapses of neurons and may be implicated as a regulator of synapse formation, neural plasticity. Aβ42 (metabolized product of soluble Aβ) has been reported to be lower in HIV patients in comparison to both HIV-positive non-dementia patients and HIV-negative patients with dementia. Tau is a structural neuronal protein. There are 2 dominant forms that cannot be measured: total tau (t-tau) and phosphorylated tau (p-tau). Elevation of CSF t-tau reported as an indicator of neural injury [16]. Matrix metalloproteinases (MMPs) are a family of neutral proteases that are important to normal development and have been implicated in many pathological processes. MMP-9 has been shown to be elevated in HIV-positive subjects with neurological deficit [17].

However, despite many years of research, still there is a lacuna in biomarkers that can measure and predict the onset of HIV-1-associated neurocognitive disorders. Biomarkers of HAND are more or less similar compared to the biomarkers of other neurodegenerative disorders because many of the molecular mechanisms are akin in these diseases. Increasing incidence of neurodegenerative disorders is already on the rise due to the introduction of the retroviral therapy and preventive measures in HIV patients, even though the incidence of the severe dementia is substantially reduced after the introduction of HAART. Proteomic profiling experiments utilizing cells of the CNS and in vitro systems have begun to emerge and have the potential to generate new and highly valuable information about the phenotype(s) alterations of HIV infecte as well as uninfected cells. There is a possibility that this avenue will be explored more in some HAND and CNS infection patients without concomitant increase in p-tau reported as an indicator of neural injury [16].

REFERENCES


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