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Commentary

Predictive biomarkers for cognitive decline during progressive HIV infection

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HIV-associated neurocognitive disorder (HAND) is a common viral co-morbidity. It remains prevalent despite the dramatic improvements in quality and length of life that follows antiretroviral therapy (ART) [1]. The cognitive, behavioral and motor dysfunctions that characterize HAND are differentiated by symptom severity. They include asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia (HAD) [2]. Prior to ART, severe cognitive impairments (CI), reflected by HAD was the common disease manifestation of progressive viral infection. As of today, mild signs and symptoms dominate. These follow ART induced virus suppression and include subtle short-term memory and decision-making abnormalities alongside behavioral and motor skill impairments. What causes CI is broad encompassing co-morbid diseases, antiretroviral and abused drugs, mental health-related issues, metabolic disorders, psycho-social disease consequences and the virus itself [3,4]. The latter reflect inflammation produced as a result of virus infected mononuclear phagocytes (MP; macrophages and microglial) activation. Indeed, secretory MP products (for example, tat, gp120 and others), neuronal growth factor blockade and immune senescence result from viral infection [5–7]. It is well known that HIV-1 infects the central nervous system (CNS). This occurs soon after viral acquisition resulting in neuronal damage and consequent loss. This occurs prior to the development of disease-associated signs and symptoms. Infected MP and CD4+ T effector cells cross the blood-brain barrier (BBB) which can then infect primary CNS MP and to a lesser degree astrocytes [1]. These cells, following virus-induced activation, release chemokines and cytokines that further disrupt the BBB and affect ingress of an increasing number of inflammatory lymphocytes and monocyte-macrophages into the brain. It is accepted that for ANI, MND or HAD, any or all, of these mechanisms may result in such alterations of the brain's homeostatic environment and produce the resultant neurotoxicities from inflammation. These processes lead to HAND in up to a half of ART-treated and virus-infected people. Thus, the presence of inflammation and linked neurodegeneration in both the brain as well as the cerebrospinal fluid of infected and ART-treated people affects production of disease biomarkers [6]. Each also underscores the strong associations between inflammation and disease. Several groups propose several of disease inflammatory biomarkers including, but are not limited to, platelet activating factor, arachidonic acid and its metabolites, granulocyte macrophage colony stimulating factor, interleukin-6, tumor necrosis factor alpha (TNF-α) and matrix metalloproteinases 1 and 7 (reviewed in 1). Their presence also leads to the changes seen in magnetic resonance imaging (MRI) and neuropsychological tests [4,6–8]. Each yield inter-individual variations and reflects cognitive function, demographics and neurocognitive dysfunctions. However, in the current ART era, inflammation is localized probably close to viral reservoirs and minimal quantities of these inflammatory factors reach the CSF or serum. Thus, there is an immediate need to uncover diagnostic and prognostic biomarkers for HAND and to separate out the plethora of co-morbid conditions, substance abuse disorders and immune deterioration in the face of ART. This is especially important in differentiating HAND from other brain disorders. To this end, neurofilament light (NFL) chain concentration, soluble amyloid precursor protein alpha and beta (sAPPα and β) and tau proteins (total tau, phosphorylated tau), resting-state functional MRI, and prepulse inhibition have emerged as test platforms to more precisely assess virus-induced CI [7–9]. Although significant genotypic differences have been observed in NFL chain concentration, sAPPα, sAPPβ, tau proteins, and resting-state MRI a myriad of limitations in their sensitivity and specificity have reduced their impact as HAND biomarkers. Added to such limitations is the absence of any underlying clinical event that would predict whether or not an infected person would ultimately develop HAND. These include questions for whether HIV progression and brain penetrance of antiretroviral drugs predicts neurological

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impairments. Moreover, whether the abilities of drugs to reach infected cells and the role of restricted viral brain infection leads to disease all remain uncertain for cause and effect of neurological aberrations. Thus, the article by Velasquez and colleagues in the current issue of *EBioMedicine* is timely as it addresses each and all of these issues [10]. The important study offers a number of novel findings. The researcher's uncover new biomarkers by showing that circulating levels of ATP and PGE_2 while below the detection limit, in the uninfected, are easily demonstrated during viral infection. Notably, pannexin-1 (Panx-1) a host protein linked to viral cell entry and replication was found to be linked to ATP. Indeed, opening of Panx-1 was found associated with the release of ATP into the extracellular space. During disease conditions that include HIV-1 Panx-1 channels open affected by inflammation and viral infection. Interestingly, no Panx-1 channel opening was observed in healthy conditions. In further support of the importance of this pathway they show that cells from HIV-infected individuals have spontaneous channel openings and that this occurs even in the presence of suppressed virus and normal CD4+ T cell counts. The results serve to highlight the importance of the channels in viral persistence. HIV-infected people show circulating levels of PGE_2 and ATP and both are released through open Panx-1 channels. Most importantly, ATP levels proved to be predictive of CI. The importance of these findings was affirmed by demonstrating that ATP was associated with BBB compromise in a Panx-1 dependent manner. Taken together, the results of this study indicate that circulating ATP levels may be a useful predictor of CI and possibly that blocking Panx-1 channels could lead to novel therapeutics by reducing the common chronic inflammation seen in infected individuals.

While the mechanism of increased levels of ATP seen in HIV-infected population is not known there the findings were selective as no association of ATP levels were seen in stroke or other infections as well as genetic factors, ethnicity or gender. While true, the limited number of samples analyzed do not preclude comorbid conditions and most notably mental health related conditions and use of abused drugs. The linkages between disruption of neural and barrier function and cognitive compromise are also not known. A surprising result was that all HIV infected samples analyzed showed a specific type of PGE_2 and ATP associated inflammation but not TNF-α or IL1β. While of interest the absence of broad comparisons for other known biomarker predictors remained incomplete. As neuroinflammation and neurodegeneration continue, individuals develop worsening degrees of neurocognitive impairment and dementia and as such the precise association between ATP and disease progression remains to be completed in future studies as its relationship to other forms of cognitive dysfunction such as Alzheimer's disease. Nonetheless, the authors are to be congratulated for their important finding in uncovering a novel pathway that predicts the unique aspects of HIV-associated CI seen the face of ART-induced viral suppression. We look forward to the next stage of these important findings towards a clinical biomarker for HAND.

Declaration of Competing Interest

None.

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