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Role of the immune system in HIV-associated neuroinflammation and neurocognitive implications ☆

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ABSTRACT

Individuals living with HIV who are optimally treated with combination antiretroviral therapy (cART) can now lead an extended life. In spite of this remarkable survival benefit from viral suppression achieved by cART in peripheral blood, the rate of mild to moderate cognitive impairment remains high. A cognitive decline that includes impairments in attention, learning and executive function is accompanied by increased rates of mood disorders that together adversely impact the daily life of those with chronic HIV infection. The evidence is clear that cells in the brain are infected with HIV that has crossed the blood–brain barrier both as cell-free virus and within infected monocytes and T cells. Viral proteins that circulate in blood can induce brain endothelial cells to release cytokines, invoking another source of neuroinflammation. The difficulty of efficient delivery of cART to the central nervous system (CNS) contributes to elevated viral load in the CNS, resulting in a persistent HIV-associated neurocognitive disorders (HAND). The pathogenesis of HAND is multifaceted, and mounting evidence indicates that immune cells play a major role. HIV-infected monocytes and T cells not only infect brain resident cells upon migration into the CNS but also produce proinflammatory cytokines such as TNF and IL-1ß, which in turn, further activate microglia and astrocytes. These activated brain resident cells, along with perivascular macrophages, are the main contributors to neuroinflammation in HIV infection and release neurotoxic factors such as excitatory amino acids and inflammatory mediators, resulting in neuronal dysfunction and death. Cytokines, which are elevated in the blood of patients with HIV infection, may also contribute to brain inflammation by entering the brain from the blood. Host factors such as aging and co-morbid conditions such as cytomegalovirus co-infection and vascular pathology are important factors that affect the HIV-host immune interactions in HAND pathogenesis. By these diverse mechanisms, HIV-1 induces a neuroinflammatory response that is likely to be a major contributor to the cognitive and behavior changes seen in HIV infection.

1. Introduction

> "A 24-year-old unmarried woman presented with 9 months' history of abnormal behavior and depressed mood, 6 months' history of tremulousness of both hands, and history of urinary and bowel incontinence for 3 months. She stopped taking care of self and started showing disinterest and apathy toward day-to-day activities... impaired sustained attention and recent memory... Magnetic resonance imaging of the brain revealed diffuse cortical atrophy... The CSF analysis showed clear acellular fluid... in view of the relatively rapid onset of cognitive impairment with prominent motor symptoms, the patient was checked for HIV and was found to be positive... diagnosed with HIV-associated dementia. However, she died suddenly before we could initiate antiretroviral therapy" (case report, Verma and Anand, 2014).

More than 30 years have passed since the epidemic presentation of opportunistic infections and other unusual diseases among previously healthy homosexual men in the U.S. It was later termed acquired immunodeficiency syndrome (AIDS) (see Fauci, 2008; Rosca et al., 2012 for a historical perspective). The causal link was made to a retrovirus called human immunodeficiency virus (HIV) (Barre-Sinoussi et al., 1983; Popovic et al., 1984). Over 25 million HIV-infected (HIV+) people have since died, and over 30 million people are currently living with HIV/AIDS worldwide, one million of whom are in the U.S. The total number of people

☆ *Research highlight:* This review highlights the HIV-immune interactions, leading to neuroinflammatory responses, which are likely key in the pathogenesis of HIV-associated neurocognitive impairment.

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living with HIV infection in the U.S. has increased in spite of stable numbers of new cases (Center for Disease Control HIV Statistics), which indicates improved survival attributable to effective therapy. As the population with chronic HIV infection grows, more attention must be given to the persistent symptoms that affect a high percentage of individuals living with HIV infection, including neurocognitive impairment (NCI).

It is now widely recognized that microbial infections of a non-CNS origin have an impact on the central nervous system (CNS) and that the immune system plays a major role that is both protective and pathogenic. Over the years, central and peripheral nervous system complications due to HIV infection have been called AIDS dementia complex, HIV encephalopathy, HIV-associated dementia (HAD), neuroAIDS and, more recently, HIV-associated neurocognitive disorders (HAND) (Antinori et al., 2007), reflecting its symptom presentation and severity through the development and evolution of antiretroviral treatments (ART). In this review the term HAND is used, especially, to describe mild and moderate forms of NCI that are observed more often than severe dementia ("HAD") among HIV+ individuals treated with combination antiretroviral therapy (cART). Before ART was available, over half of HIV-infected individuals suffered from HAD, a severe impairment that includes motor dysfunction. Even being treated with the initial ART (monotherapy), up to 50% of HIV-infected individuals exhibited various degrees of NCI (Grant et al., 1992). cART (or highly active ART, HAART) led to dramatically improved survival of HIV-infected patients and decreased prevalence of overt dementia. Meanwhile, the incidence of HIV-related mild cognitive impairment persists with a significant impact on mortality (Ellis et al., 1997a) and quality of life (Heaton et al., 2010). In addition, increased postmortem findings of HIV encephalopathy in the cART era (Neuenburg et al., 2002) imply that prolonged survival leads to a higher number of HIV+ patients continuing to suffer from NCI during the course of their "chronic" disease. Despite great gains in knowledge, much work remains to clarify the cellular and molecular underpinnings of NCI among the HIV-infected, which will inform effective prevention and treatment strategies of HAND.

This review focuses on host immune responses to HIV and their impact on the CNS and neurocognitive function. First, clinical presentations of HAND are discussed. Current knowledge of the pathogenesis of HAND in humans, focusing on immune activation and neuroinflammation, is discussed as are animal and *in vitro* studies that reveal HIV viral and cellular processes. A particular emphasis is given to the mechanisms of HIV transport and immune cell migration across the blood brain barrier (BBB) as critical processes in HIV-induced CNS pathology. Common co-infections among HIV+ individuals such as cytomegalovirus (CMV) are discussed briefly for their documented psycho-neuro-cognitive impact and immune system implications, as they shed light on HIV-related neurocognitive pathology. Lastly, host factors such as aging are highlighted for future research, as growing evidence indicates the importance of HIV-host interactions in the pathogenesis of HAND. Acute infections of the CNS or opportunistic infections by other pathogenic microbes secondary to HIV infection are outside the scope of this review. The clinical manifestations of various CNS infections, including HIV, especially in the aging population, are reviewed elsewhere (see Ellis et al., 2014, chapter 18).

2. Clinical features of HIV-related neurocognitive impairment

Cognitive, behavioral and motor impairments significantly affect daily living of individuals with advanced HAD: inability to complete complex tasks, delayed speech output, loss of initiative, impaired fine motor speeds and skills, unsteady gait, etc. (Ances and Ellis, 2007). However, these severe cases of HAD are becoming increasingly uncommon since the advent of highly effective cART (Joska et al., 2010). Meanwhile, it is troubling to many living with HIV infection and care providers that the rate of mild to moderate cognitive impairment remains high (over 50%) even among individuals who have achieved viral suppression as a result of optimal treatment (Heaton et al., 2011; Robertson et al., 2007). Indeed, the rates of HAND among individuals with mild HIV symptomatology (i.e., CDC stage A based on the previous classification) are higher in the cART era in comparison to those in the pre-cART era (Heaton et al., 2011).

Subtle presentations of mild to moderate HAND and little or gradual change over an extended period of time lead to difficulty in detection and monitoring of the symptoms, necessitating the need for comprehensive and sensitive, yet practical evaluation tools. Periodic administration of comprehensive neuropsychological (NP) tests with proper normative corrections is useful in diagnosing and evaluating the progression of HAND (Cysique et al., 2011). Validation of truncated NP tests is also important for the cases in which a comprehensive NP test is unavailable. Complementary evaluations such as brain imaging and analyses of soluble markers in cerebrospinal fluid (CSF) can be potentially informative in characterizing HAND. The results of a comprehensive NP testing battery provide domain-specific (e.g., executive function, psychomotor, verbal learning, etc.) and overall neurocognitive performance evaluations that can be followed over time, enabling objective measurements of time-, disease progression- and treatment-dependent changes. Among different domains of NP function, deficits in motor speed, information processing speed and verbal fluency were more often observed before the cART era, whereas impaired learning and executive function are more frequently observed among the individuals treated with cART (Heaton et al., 2011). Both lifetime and current depression rates are greater in HIV+ compared to seronegative individuals, and among HIV+ individuals significantly higher rates of current depression are found in more advanced HIV disease (i.e., CDC-B and C stages) (Heaton et al., 2011). Moreover, HAND is associated with current depressive symptoms regardless of cART treatment status or types (Ances and Ellis, 2007). Thus, potential confounding conditions such as depression and substance abuse should be considered in interpretation of NP test results.

Mild to moderate cognitive impairment rarely progresses to dementia in HIV disease managed with cART, leading to the notion that the clinical course of HAND differs from that of typical neurodegenerative diseases such as Alzheimer's disease (Valcour et al., 2011). At the same time, some of the hallmark neuropathology of typical neurodegenerative diseases have been observed among HIV+ individuals, such as the β-amyloid plaques of Alzheimer's disease and the α-synuclein deposits of Parkinson's disease (Andras and Toborek, 2013; Esiri et al., 1998; Khanlou et al., 2009). Structural brain imaging of individuals with HIV and suspected NCI shows impact on deep grey matter structures and subcortical regions (Valcour et al., 2011) and cerebral atrophy with ventricular enlargement (Ances and Ellis, 2007). Others report neuropathological findings in cortical regions, especially in the cART era (Clifford and Ances, 2013; Heaton et al., 2011). Furthermore, some studies report brain imaging findings in association with neurobehavioral presentations: white matter changes were associated with presentation of apathy (Hoare et al., 2010). Older individuals with HAND exhibited less activation in the left frontal regions ("attention network") and poor performance during the cognitive tasks that required increased attention compared to HIV- and HIV+ individuals without NCI (Chang et al., 2008).

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