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HIV-Associated Neurocognitive Disorders and the Impact of Combination Antiretroviral Therapies

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Abstract

HIV-associated neurocognitive disorders (HAND) are the most common preventable and treatable cause of dementia. While the incidence of the most severe form of HAND, HIV-associated dementia, has decreased since the introduction of combination antiretroviral therapy (cART), the prevalence of less severe forms of HAND has continued to rise. HAND leads to a subcortical dementia consisting of a triad of cognitive, behavior, and motor dysfunction. No single laboratory test can establish HAND, but ancillary studies including neuropsychological testing, neuroimaging studies, and cerebrospinal fluid (CSF) analysis are useful for supporting or refuting the diagnosis. More recent evidence has suggested that higher central nervous system–penetrating cART may lead to greater suppression of CSF HIV viral loads and improved cognition. Because viral control generally has been successful without eliminating cognitive dysfunction, further clinical studies that assess adjunctive neuroprotective drugs are likely to be required.

Introduction

Since the early description of HIV, the neurocognitive manifestations of infection have been recognized. HIV-associated neurocognitive disorders (HAND) were originally described in the 1980s as subacute encephalitis [1]. The term *AIDS dementia complex* (ADC) originated in 1986 after clinical and neuropathologic characterization of 46 AIDS patients with impaired mentation [2,3]. The authors observed a triad of cognitive, motor, and behavioral symptoms in nearly 25% of HIV-infected subjects, with many eventually developing dementia. On autopsy, subcortical changes were seen with characteristic white matter pallor and rarefaction accompanied by lymphocytic and macrophage infiltration [4].

In response to these observations, the American Academy of Neurology AIDS Task Force in 1991 published criteria for HAND within the central nervous system (CNS) [5]. Two major categories were created: 1) a more severe form called HIV-associated dementia (HAD; previously known as ADC) and 2) a less impaired form called HIV-associated minor cognitive/motor disorder (MCMD). For both disorders, diagnosis required that symptoms impair everyday functioning. These criteria were validated through longitudinal studies that showed subjects with HAD had shorter life span [6,7].

Prior to the introduction of antiretroviral medications, a balance existed for patients with HAD between a high incidence and mortality due to AIDS-related complications [8]. The advent and widespread initial use of monotherapy (single agents such as zidovudine) and subsequently combination antiretroviral therapy (cART) reduced the incidence of HAD [9]. However, the prevalence of milder HAND has increased because individuals live longer with the disease and incompletely recover [10,11]. The course of these less severe cases of

HAND appears variable with stability, fluctuations, progression, or sometimes regression [12]. cART has dramatically reduced the impact of opportunistic infections. Instead, substance abuse, hepatitis coinfection, neuropsychiatric comorbidities, and neurotoxic effects of cART have become the focus of differential diagnoses.

To account for these changes, the diagnostic criteria for HAND were recently revised. Criteria for HAD and MCMD were based primarily on severity of impairment on neuropsychological (NP) testing and on degree of functional impairment on activities of daily living with differentiation occurring according to the severity in these domains. Milder forms of HAND have prevailed since the advent of cART. HAND has now been divided into three conditions: asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and HIV-associated dementia (HAD) [13••]. Individuals with ANI have demonstrable (and usually mild) cognitive impairment demonstrated by formal NP testing without any observed abnormalities in everyday functioning. The diagnosis of MND is similar to that for MCMD but requires not only mild to moderate NP testing abnormalities but also impairment in activities in daily living. Subjects with HAD have moderate to severe NP testing impairments and marked difficulty in performing activating of daily living. Exclusion of delirium or comorbid conditions that might explain the dysfunction is required for these diagnoses.

Neuropathogenesis

HIV typically reaches the brain soon after initial infection, possibly shortly after seroconversion [14]. Clinical evaluation of subjects at the time of their HIV seroconversion noted the presence of meningitis or meningoencephalitis. In some of these cases, HIV p24 antigen was isolated from the cerebrospinal fluid (CSF) near the time of seroconversion [15].

One theory proposed for possible viral entrance involves infected monocytes trafficking across the blood–brain barrier (BBB): a “Trojan horse” mechanism. After these infected monocytes have crossed the endothelium, they settle as infected perivascular macrophages. It has been suggested that macrophages spread virus by cell-to-cell contact with microglia cells [16]. Another theory for viral entry could be cellfree virus directly crossing the BBB or entering through the CSF. The presence of productive virus in endothelial and choroids plexus cells supports these theories [17]. Overall, macrophages in the perivascular spaces and multinucleated giant cells (fused macrophages and microglia cells) are the major brain cell types that support viral replication in the brain. Productive infection of neuroectodermal-derived cells (neurons, astrocytes, and oligodendrocytes) remains rare [18].

Two views have been postulated concerning the dynamics of HIV entering the CNS [19]. One plausible view is that the CNS is exposed to repeated transitory contacts of virus transported across the BBB via monocytes. A dynamic viral equilibrium exists between the CNS and other loci of infection within the body. Activated inflammatory cells freely enter and leave the brain and are likely trafficking during the long duration of systemic HIV infection. A different viewpoint holds that the CNS could also serve as a relatively autonomous reservoir producing virus locally, with the opportunity for independent evolution under different immunologic and pharmacologic conditions than exist outside the CNS [20]. Most likely, both of these situations exist with one subtype dominating the other during different stages of the infection.

In both scenarios, viral replication surely occurs often in the CNS. With repeated exposures and enhanced viral replication within microglia, a complex cascade is instigated within the brain. Viral proteins are released within brain tissue. Microglia and astrocytes are stimulated by these proteins to produce chemokines, cytokines, and other inflammatory mediators (ie,

tumor necrosis factor- α , nitric oxide, neopterin, β_2 -microglobulin, and quinolinic acid) that regulate cell interactions for normal functioning [21–23]. These cell-encoded signals promote increased HIV replication in microglia cells and stimulate the further release of viral proteins. This may have a toxic effect on neurons, leading initially to neuronal dysfunction and eventually to neuronal loss.

Neuropathological evaluation of brain tissue of HIV-infected individuals is typically characterized by relatively nonspecific features such as white matter pallor, microglial nodules, and gliosis [12]. Multinucleated giant cells are more distinctive for advanced disease and are rarely seen the era of cART. However, when a constellation of these features are present in the setting of known HIV infection, a characteristic neuropathological signature is observed. Pathological changes are typically mild, even in HAD, with abnormalities most prominently occurring in central white matter, frontal cortices, basal ganglia, thalamus, and brain stem [24]. Cognitive status generally does not correlate with neuronal loss but instead with degree of damage to dendrites and synapses [25]. The overall scarcity of infected cells and the imprecise correlation between the severity of pathology and the degree of dementia suggest that multiple factors most likely play a role in neuropathogenesis [26].

Diagnosis

Clinical features and course

HAND is characterized by a triad of cognitive, behavioral, and motor dysfunction. During the early stages, the general neurologic examination is often normal, with patients noting mild difficulties in concentration, attention, and memory [27]. Patients may experience reading difficulties with problems stemming from loss of concentration (thus requiring rereading) rather than comprehension. Affected individuals may be easily distracted, lose their train of thought, and require repeated reminders. Symptoms may intrude on activities of daily living such that common tasks take longer and become more laborious. Motor symptoms are typically mild and consist of slowed repetitive movements, clumsiness, unsteady gait, or balance problems.

Due to cART, more severe forms of HAND, such as HAD, are rare. In these more severe cases, cognitive and motor dysfunction are often quite distinct. Activities of daily living often cannot be adequately completed without assistance. Speech output is delayed, with long pauses when the patient is answering questions. Thought and emotional content are often impoverished, with behavioral changes causing a loss of spontaneity and initiative. Abulia and social withdrawal may be so striking that patients are mistakenly diagnosed with severe depression [28]. Motor abnormalities are usually prominent due to unsteady gait balance. The neurologic examination often shows frontal release signs, spasticity, and brisk deep tendon reflexes.

Because HAD is now relatively uncommon, research is now focused on identifying and distinguishing the milder types of HAND: ANI and MND [13••]. Conventional bedside cognitive testing using instruments such as the Folstein Mini-Mental State Examination is insensitive to deficits of HAND. The HIV Dementia Scale was developed as a rapid screening test to assess for HAD [29]. This battery assesses psychomotor processing speed, verbal memory, constructional abilities, and executive function. Although it is useful for assessing HAD, its utility in assessing ANI and MND remains limited [30].

Differential diagnosis

The differential diagnosis must be quite broad when considering neurologic impairment in an HIV-infected patient (Table 1). Many subjects have a prior history of psychiatric

disorders [31]. Substance abuse and/or withdrawal can lead to transient changes in cognition that complicate the diagnosis. CNS opportunistic infections can lead to cognitive and neuropsychiatric symptoms. Hepatitis C infection and treatment with interferon or ribavirin can also lead to depression and cognitive dysfunction in many HIV-coinfected individuals [32]. In addition, subjects with end-stage liver disease and cirrhosis may experience delirium (“hepatic encephalopathy”) superimposed on cognitive complaints. Antiretroviral drugs can also cause neuropsychiatric changes, with the most common offending agent being efavirenz. Vivid dreams and vestibular changes are typically seen early after initiation of this medication [33]. No single laboratory test establishes the diagnosis of HAND, but ancillary studies such as NP testing, neuroimaging studies, and CSF analysis may be useful for supporting or refuting it.

Neuropsychological testing

For optimal sensitivity, an NP examination should include tests of the following ability domains (with at least two test measures per domain): verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; and motor skills [13•]. Notably, NP testing is nonspecific, and there is no reliable pattern that can be specifically attributed to HIV-related neurologic changes. Thus, diagnosis must also be informed by means including clinical history, examination, and laboratory testing. Furthermore, comprehensive NP testing is distasteful to many patients in HIV clinics. It is time intensive, expensive, and difficult to organize, and its use can be problematic in a variety of circumstances. Because norms need to consider a large variety of social, educational, and environmental factors, local norms are required in the developing world and are often unavailable. Thus, use of NP testing in developing nations where HIV is most prevalent is problematic, at a minimum requiring additional investment to develop appropriate norms. Despite these limitations, NP testing remains a critical part of the research assessment of a HAND.

Neuroimaging

Structural MRI techniques play a critical role in differentiating HAND from other disorders. Conventional anatomic scans of HIV-infected individuals using T1- and T2-weighted imaging may show cerebral atrophy with corresponding ventricular enlargement [34]. Patchy confluent areas of high signal intensity within the white matter are often seen on fluid-attenuated inversion recovery scans. Magnetic resonance spectroscopy also accesses metabolite changes within selected brain regions. A reduction in n-acetyl-aspartate, a marker of mature neurons and their axonal processes, is often accompanied by an increase in choline and myoinositol, reflecting increased cell turnover and inflammation [35,36]. Diffusion tensor MRI can noninvasively evaluate the structural displacement of water molecules. Whole brain fractional anisotropy, a measure of the direction-dependent mobility of water molecules, is significantly diminished in HIV-infected subjects and correlates with degree of neurocognitive impairment [37].

More recently, functional MRI (fMRI) techniques have been used to evaluate HIV-related brain dysfunction. The blood oxygen level-dependent (BOLD) technique has demonstrated decreased activation in areas commonly associated with attention for a simple cognitive task and increased activation in adjacent and contralateral brain regions. These results may reflect reduced efficiency in typical attention networks and recruitment of additional neural areas [38]. In addition, the novel technique of arterial spin labeling has shown that baseline measurements of resting cerebral blood flow inversely correlate with degree of neurocognitive impairment [39•]. It seems likely that the application of multimodal neuroimaging will have an increasing role in understanding the biology of HAND. However, given the resources required to apply it clinically, this technique will be reserved

for use in helping to understand the disease in the developing world, where HIV is most prevalent.

Cerebrospinal fluid

Analysis of CSF in HIV infection can also assist in the diagnosis of HAND. Like neuroimaging, CSF findings are particularly critical in ruling out confounding causes, but the discovery of reliable diagnostic markers has been elusive [40]. However, lumbar puncture is a remarkably safe procedure that in experienced hands is well tolerated and requires only modest resources. The introduction of atraumatic needles has vastly reduced the incidence of post-lumbar puncture headaches and made repeated outpatient CSF examinations practical. Important tests include opening pressure, culture (mycobacterial and particularly fungal) cell count, protein, cryptococcal antigen and, if available and appropriate, polymerase chain reaction testing for HIV RNA or for DNA of toxoplasma, cytomegalovirus, Epstein-Barr virus, JC virus, or herpes viruses. The presence of HIV-1 in the CSF alone is not reliable for the diagnosis of HAND. HIV CSF viral load can often be detected within both neurologically normal and impaired HIV-infected patients. Prior to cART, a correlation existed between higher CSF HIV RNA viral loads and worse NP in subjects with more advanced disease (blood CD4⁺ lymphocyte count < 200/ μ L) [41]. However, since the introduction of cART, CSF HIV RNA viral load has become a less reliable marker because most patients generally attain undetectable values by current clinical assays. Exploration of the value of ultrasensitive assays with limits of detection down to very low levels may give insight into hypothesized low levels of ongoing viral replication in the CNS and remains an area of future research [26]. Except for identifying alternative diagnoses, CSF analysis in patients with HIV has been largely ignored as a diagnostic tool. It is possible that characterization of alterations in CSF biomarkers at different stages of infection could provide a greater understanding of brain dysfunction due to HIV [42•]. A single CSF biomarker may not meet all needs for characterizing HAND. Instead, a combination of CSF biomarkers might be more suitable with markers of different types having complementary diagnostic importance. Recent studies have shown that both markers of immune activation (neopterin and β_2 -micro-globulin) and neuronal destruction (neurofilament light chain) are elevated in HAD [43•].

Another area of active interest in CNS markers in the past few years has centered on metabolism of beta-amyloid. The possibility that chronic immune activation in the CNS during HIV infection might also trigger some form of degenerative disease prompted evaluation of markers typically associated with Alzheimer's disease. An accumulation of brain beta-amyloid is accompanied by significant decline in CSF beta-amyloid in subjects with Alzheimer's disease. Similar findings have been observed for HAD and not asymptomatic subjects, with a decline in beta-amyloid being the most reliable of the findings [44•].

Treatment

Highly potent cART has proven to achieve long-term control of the virus, with immunologic improvements and survival benefits. Typically, multiple highly active antiretroviral medications from different classes attack several points in the viral life cycle. By combining drugs from different classes, cART exerts selection pressure on multiple viral genes, reducing the likelihood that mutations will arise in the right combinations to render resistance to a single agent or drug class. The goal of cART is to reduce viral replication and in turn reduce CD4 lymphocyte destruction. As a result, significant restoration of immune function can occur and disease progression is slowed or arrested. Unfortunately, some patients receiving cART fail to achieve full suppression due to drug resistance or inability to adhere to regimens [45].

Recently, the clinical entity of immune reconstitution inflammatory syndrome (IRIS) has been noted shortly after initiation of cART. The abrupt increase in immune surveillance, most notable when the baseline compromise is quite severe and response to therapy brisk, can result in pathologic inflammatory reactions. IRIS leads to a paradoxical clinical deterioration, as individuals can have a worsening of manifestations of underlying infection or an unmasking of a subclinical infection as CD4 counts rise and HIV RNA viral load drops. IRIS can result in clinically significant morbidity and even mortality and may involve any organ system, including the CNS. The clearest examples of IRIS relate to underlying opportunistic conditions in the CNS, most prominently cryptococcal meningitis or progressive multifocal leukoencephalopathy. However, there are cases of clinical deterioration that may relate to an IRIS response to HIV encephalitis, a possibility that has rarely been clearly documented but has considerable theoretical importance. There are no tested guidelines for the prevention or diagnosis of IRIS. Empirical trials of steroids have been used, but no consensus exists, and clinical trials are required to determine optimal treatment and management [46••].

Considerable evidence suggests that cART can assist in restoring neurocognitive function in HIV-infected individuals [45]. However, consensus treatment guidelines for HAND have not been formulated. Current recommendations for initiating or changing cART primarily depend on plasma viral load and HIV systemic disease indicators regardless of the status of the CNS infection. If repeated infection and inflammation within the brain underlies the neuropathogenesis of HAND, it may be beneficial to have specific cART regimens that are targeted to the CNS.

The CNS evolved to provide isolation from exogenous, potentially toxic molecules that might be deleterious to brain function. The BBB is achieved by capillaries with tight junctions on endothelial cells, in addition to a lamina propria and lining of endothelial cells by astrocytic foot processes, together preventing many compounds from crossing into the brain. Despite considerable research, controversy remains about whether drug penetration into the CNS is clinically important for HIV. It has been recently demonstrated that HAND-affected individuals initiating a higher CNS-penetrating cART regimen are more likely to successfully suppress CSF HIV viral load. Furthermore, individuals who achieved CSF suppression (viral load < 50 copies per milliliter) had better neurocognitive outcomes [47••]. BOLD fMRI has also provided evidence consistent with differential functional efficacy of contrasting cART regimens in the brain, as HIV-infected individuals on lower central CNS-penetrating cART regimens had significantly greater BOLD fMRI response amplitudes than HIV patients taking higher CNS-penetrating cART or seronegative controls. The observed increase in the BOLD fMRI response in HIV-infected subjects on lower CNS-penetrating cART may reflect continued HIV replication in the brain leading to increased oxidative stress and associated metabolic demands (Fig. 1) [48].

These findings suggest that neurocognitive outcomes of cART may be enhanced by the planned application of a drug selection and clinical monitoring strategy that optimizes penetration across the BBB. Formal clinical trials for adequately evaluating HAND treatment strategies represent an ongoing challenge to the field, particularly in an era when multiple new classes of drugs are being introduced, with little attention to their properties relative to the nervous system.

In parallel with efforts to enhance the antiviral therapy used for the neurologic manifestations of HIV, ongoing work has focused on the likely neuropathogenesis of functional changes in the nervous system. It is possible that neuroprotective therapy might be needed over time even when optimal ART has been used. Exploratory trials have focused on probable mechanisms of neurologic pathology, using drugs believed to be

neuroprotective, with in vitro models suggesting activity against HIV-associated neuropathologic processes. Recent trials have sought to block apoptotic cell death, which is likely enhanced in chronic HIV brain infection, through application of transdermal selegiline [49]. More recent efforts are testing minocycline, which may have several mechanisms, including anti-inflammatory mechanisms, suppression of p38 mitogen-activated protein kinase, antioxidant activity as an inhibitor of inducible nitric oxide synthase, antiapoptotic mechanisms, and inhibition of matrix metalloproteinases. The potential efficacy of minocycline is supported by demonstration of benefit in the simian immunodeficiency virus experimental model of retroviral encephalitis [50].

Conclusions

The characteristics of neurocognitive impairment due to HIV have changed with the advent of cART. What was once an almost uniformly fatal illness frequently associated with a severe subcortical dementia is now a chronic disease requiring long-term medical management. However, as the prevalence of HAND continues to rise there remains a significant burden of lesser degrees of neurocognitive impairment that persist in individuals who now may live for many years with effective cART. Therapeutic frontiers remain for optimizing the effective use of antiretrovirals into the CNS and for developing adjuvant neuroprotective therapies that can repair and protect vulnerable neurons.

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Disclosures

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Figure 1. The amplitude of the blood oxygen level-dependent (BOLD) functional MRI response for seronegative controls (SNC) and HIV-positive patients on low and high central nervous system penetration effectiveness (CPE) combination antiretroviral therapy groups. A significant difference was observed between HIV-positive patients on low CPE and high CPE combination antiretroviral therapy ($P < 0.03$). Error bars signify the SEM. (*Adapted from Ances et al. [48].*)

Table 1

Differential diagnosis of HIV-associated neurocognitive disorders

Delirium
Psychiatric disorders (primary or comorbid)
Neurodegenerative disorders (primary or comorbid)
Central nervous system opportunistic infections
Substance abuse or withdrawal (including alcohol, methamphetamine, marijuana, and cocaine)
Hepatitis
Neurotoxic side effects of combination antiretroviral therapy or other prescribed medications
Medication interactions
Endocrine abnormalities