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Update on HIV-associated Neurocognitive Disorders

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Abstract

Neurocognitive disorders are a feared complication of HIV infection, especially in the post anti-retroviral era as patients are living longer. These disorders are challenging in terms of diagnosis and treatment. The clinical syndrome has evolved driven in part by comorbidities such as aging, drug abuse, psychiatric illnesses, and a metabolic syndrome associated with the use of antiretroviral drugs. Additionally some individuals may develop a fulminant immune reconstitution syndrome. Hence management of these patients needs to be individualized. The focus of research in the HIV field has recently switched towards elimination of the HIV reservoir as a means of combating long-term HIV complications. However these approaches maybe suitable for limited populations and might not be applicable once the HIV reservoir has been established in the brain. Further, all clinical trials using neuroprotective or anti-inflammatory drugs for treatment of HIV-associated neurocognitive disorders have been unsuccessful. Hence neurological complications of HIV infection represent the biggest challenge facing HIV researchers and there is a critical need for developing new diagnostics and approaches to treatment for these disorders.

Keywords

human immunodeficiency virus; HIV-associated neurocognitive disorders; compartmentalization; antiretroviral; latency

Introduction

Over 40 million people worldwide are infected by HIV-1 (UNAIDS/WHO) [1], and while HIV-1 is most well known for its devastating effects on the immune system and the resulting AIDS, it can involve any level of the neuro-axis [2]. In this review, we will focus on updates related to HIV-associated neurocognitive disorders (HAND). Despite the success of combination anti-retroviral therapy (cART) in controlling HIV infection as evident by decreased viral loads to undetectable levels and increasing CD4 count back to normal, and despite a decrease in the risk of opportunistic infections and mortality, HAND have

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Compliance with Ethics Guidelines

Conflict of Interest

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Human and Animal Rights and Informed Consent

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continued to affect HIV-infected populations [3]. Neurocognitive impairment even in the milder forms not only has profound socioeconomic consequences from the effects on activities of daily living and impact on employability but may have important consequences on the ability to control this pandemic. These individuals may have difficulty complying with taking medications [4] keeping up with physician appointments, may suffer from psychiatric manifestations, may have difficulty in using preventive measures for viral transmission and may be more vulnerable to sexual abuse. Certainly survival rate of patients with HAND is much lower than that of HIV-infected individuals without HAND [5]. Thus clearly our hopes of eradicating this virus or controlling its spread cannot be realized unless we pay close attention to the neurocognitive consequences of the infection and develop ways of effectively treating it.

Changes in Terminology

Many synonymous terms have been used in the past to describe the neurocognitive decline associated with HIV infection, including: AIDS dementia complex, HIV dementia, HIV encephalopathy, minor cognitive motor disorder, and HIV-associated dementia complex. The term HIV encephalitis, however, is used for the description of the pathological features of multinucleated giant cell encephalitis with HIV identified in the brain [6]. As the severe forms of neurocognitive impairment such as dementia are seldom seen in patients compliant with cART, current nosology has changed to identify individuals with milder forms of dysfunction. This requires the use of detailed neuropsychological tests and divides HAND into three categories: HIV-associated asymptomatic neurocognitive impairment (ANI), HIV-associated mild neurocognitive disorder (MND), and HIV-associated dementia (HAD) [7]. This categorization recognizes the importance of using demographically appropriate means for comparison, as well as the possible contribution from confounding conditions such as aging, depression, drug abuse, opportunistic CNS disease, or co-infection with hepatitis C virus. Conventional bedside cognitive testing using instruments such as the Mini-Mental State Examination (MMSE) or the HIV Dementia Scale which were adequate as a screening tool for patients with dementia are not reliable for revealing impairment in most patients with HAND. Comprehensive neuropsychological testing with application of appropriate normative corrections is much more sensitive and specific. One drawback of the current system is that it does not take into account psychiatric manifestations of HIV infection such as depression and psychosis.

Changing pattern of Clinical Features in post-cART era

HAND typically presents as a subcortical dementia with cognitive, behavioral, and motor decline over weeks or months, which interferes with activities of daily living and cannot be explained by another pre-existing neurological disease, severe substance abuse, or another cause of dementia. Since the era of cART, the cumulative risk of developing HAND during the course of the infection has reduced, but due to the longer survival and the subsequently increasing age of the infected individuals, the prevalence has continued to rise [3]. In 2007, the category of ANI was added to HAND. ANI refers to individuals who score one standard deviation below the mean on at least two areas of a standardized neuropsychological test; however, that impairment on testing is not causing an observable functional impairment. These patients may go on to develop symptomatic impairment in the form of MND or HAD, but the time course of cognitive change in HIV is not predictable or linear in many cases. Even with consistent treatment with cART, cognitive performance may fluctuate over time, making diagnosis more difficult; in some cases complete recovery occurs after initiation of cART [8]. MND describes an individual who demonstrates impairment on neuropsychological testing as just described for ANI but also demonstrates some type of mild impairment in daily functioning. These patients are likely to be able to continue

working, although at a reduced level of productivity or efficiency. Movement disorders, such as gait disturbance, tremor, and impairment of fine manual dexterity, may be present [9]. HAD refers to a person showing marked impairment on neuropsychological testing and in daily functioning.

Disorientation, mood disturbances, psychomotor slowing, and a decrease in attention, memory, and visuoconstructive coordination are part of the clinical picture. Motor symptoms are often mild and may consist of a slowing of repetitive movements or balance problems. Absence of focal cortical signs such as apraxias, agnosias, or aphasias assists in distinguishing the condition from cortical dementia like Alzheimer's disease. Patients with HAD have difficulty learning new information, such as word lists, but they do not show the rapid forgetting that is commonly seen in Alzheimer's disease.

The large National Institute on Mental Health cohort CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study used standardized neuropsychological tests to evaluate 857 patients from 1988 to 1995, and 937 patients from 2000 to 2007. Between the pre-ART and ART eras, fewer patients performed poorly in verbal fluency (eg, number of animals named in timed setting), speed of information processing (digit vigilance time), and motor domains (grooved pegboard test), while more patients showed deficits in learning and memory (story memory test) and executive functioning (Wisconsin card-sorting test). The domains of recall, working memory, and attention were stable across the two time periods [10]. This shift in cognitive domains most affected in patients with HIV infection has important implications for trials of adjunctive therapy, such as antioxidants or neuroprotective agents, in determining which cognitive tests to study. Whether these data reveal a greater degree of cortical impairment, rather than subcortical pathology, in HAND in the era of ART will require neuroimaging and neuropathologic correlation.

In the era of cART, some patients may also develop a progressive subacute encephalitis called CNS-immune reconstitution inflammatory syndrome (IRIS). This inflammation is driven by CD8+ T cells and presents with cognitive decline, seizures and eventually coma and death. Early recognition and treatment with corticosteroids can reverse the process (reviewed in [11]).

Laboratory Investigations

Magnetic resonance imaging of the brain may show progressive cortical atrophy and diffuse white matter changes particularly in advanced stages of the disease (Figure 1). Magnetic resonance spectroscopy may show elevation of myoinositol suggestive of inflammation or glial cell activation and decrease in N-acetyl aspartate suggestive of neuronal injury. Electroencephalogram does not show any specific changes, although generalized slowing may be seen. Occasionally seizure activity may be detected particularly in patients with IRIS. CSF may be normal or have mild pleocytosis and slightly elevated protein. Although available only in research laboratories, inflammatory markers such as cytokines and chemokines are often elevated in the CSF. In the untreated patient the markers suggest macrophage activation while in the individuals treated with antiretrovirals, the profile suggests T cell activation instead [9].

Evolution of risk factors for HAND

Interestingly, even in the pre-cART era, nearly 50% of individuals with HIV infection did not develop neurocognitive impairment, suggesting that host or viral genetic factors may play a role [3]. However, host genetic factors have not been extensively studied. Polymorphisms in apolipoprotein, cytokine and chemokine pathways and innate immune responses have been implicated in the progression of neurocognitive dysfunction of HIV-

infected individuals [12-14]. Future studies such as genome wide associations and high throughput single nucleotide polymorphisms are needed to identify the critical genes involved in HIV neuropathogenesis. This will also allow for better clinical trial design and may have implications for other neurological diseases.

In recent years, several comorbidities have been identified as important risk factors for HAND. These include drug abuse, however since most patients are poly drug abusers, the types of drugs used and frequency of drug usage may be quite variable within a single individual and among patient groups studying their effects in conjunction to HIV infection in human populations has been challenging [15]. In individuals treated with cART, a metabolic syndrome has been recognized, a prominent feature of which is dyslipidemia that may lead to vascular disease [16-19]. Microvascular disease can also result in neurocognitive impairment but the pathophysiology and treatment would be quite different from that directly due to HIV infection. Aging is another risk factor that leads to increased accumulation amyloid in the brain at a much rapid pace compared to uninfected populations [20-22]. The incidence of HAND in older individuals (>50 yrs) is much greater [23-25]. Hepatitis C infection has also been implicated in causing neurocognitive effects [26-28]. This is a frequent co-infection in HIV infected drug abusers. Thus the underlying pathophysiological mechanisms of HAND might be quite variable and HAND should not be considered a single entity (Figure 2).

Neuropathogenesis

The neuropathogenesis of HAND has also evolved over the years shaped in part by the existing comorbidities, aging of the infected populations, shift in epidemiology to drug abusing populations and effects of cART. Understanding how these variables may impact neuropathogenesis of HIV infection is critically important since therapeutic approaches may need to be tailored to these different pathophysiological mechanisms.

Recent attention has been diverted to HIV reservoirs in the brain. This renewed enthusiasm stems from the fact that a few patients claim to have been cured of HIV infection suggesting that it might be possible to purge the virus from its reservoirs. It still remains unknown if this includes the elimination of the virus from the brain. Yet important questions have been raised with regards to the timing of viral entry into the brain, the cell types infected and the ability of the virus to evolve within the brain [29].

Although, cART is successful in most cases in rapidly reducing HIV RNA to <50 copies/ml, the virus typically rebounds back quickly, sometimes as early as within two weeks of cessation of therapy. Studies with highly sensitive assays capable of detecting as low as 1 copy/ml have revealed that around 80% of patients continue to have low level viremia of around 3-5 copies/ml despite several years of cART [30, 31]. Such studies have strengthened the belief that latent infections persist in certain cells within the host and that latent viral genomes can be reactivated to produce infectious viral particles that would explain the rebound of the virus. Multiple mechanisms have been proposed as to how low level viral replication may lead to neurocognitive disorders. These include neurotoxicity and glial cell activation by viral proteins such as gp120 and Tat [32]. Once the proviral DNA has been formed and the viral reservoir has been established, antiretroviral drugs do not impact the production of Tat protein. Tat can be found in the cerebrospinal fluid and infiltrating macrophages within the brain in virologically controlled individuals [33]. Tat can also travel along neuronal pathways and thus have far reaching effects from the site of production [34]. Tat can cause T cell activation in a non-classical manner and can thus play a role in the pathophysiology of HAND or CNS-IRIS [33]. Activated T cells can cause neuronal injury by the extracellular release of granzyme B [35, 36]. The failure to eradicate HIV from its

reservoirs in host tissues is one of the major hurdles towards curing HIV infection, and cells in the brain constitute one such reservoir.

HIV-1 infection compromises the structural integrity of the intestinal tract and can cause leakage of bacteria into the blood stream. Such microbial translocation results in elevated plasma levels of bacterial lipopolysaccharide (LPS), and in HIV-infected/AIDS patients, is associated with increased monocyte activation and dementia. Additionally, it has recently reported that HAND is associated with higher systemic levels of plasma LPS [37]. The hypothesis is that HIV-1 infected patients with microbial translocation from the gut will have higher plasma LPS and thus more systemic immune activation leading to increased risk of transit of HIV-infected monocytes into end organs including the CNS [38]. Another study suggests that HIV-1 infection increases the vulnerability of the BBB in response to LPS and facilitates the transmigration of peripheral monocytes/macrophages [39].

HIV evolution in the brain with cART

Following infection, HIV RNA gets reverse transcribed into a strand of DNA that can either get integrated into the chromosomal DNA or reside episomally. Integrated viral DNA produces viral products but can be silenced by epigenetic changes, while episomal DNA may either be non-functional or may get released extracellularly. In one study the amount of unintegrated HIV DNA in the brain was found to be 6-81 fold compared to integrated DNA [40]. The levels of unintegrated DNA did not correlate with the amount of viral antigen in the brain suggesting that the unintegrated DNA was either latent or dysfunctional. In contrast, in T cells, HIV is predominantly in an integrated state [41]. The high levels of unintegrated DNA suggests that the brain maybe an important reservoir for the virus. Another study showed that the presence of unintegrated HIV DNA and HIV proteins in the brain was associated with dementia [42]. Importantly, the viral load in the brain on patients on prolonged cART may be very low [43]. Since the brain is devoid of lymphoid cells, the selective pressure on the virus is different compared to other lymphoid organs. The virus evolves in the brain to become more macrophage tropic [44] with unique brain specific mutations [45] and are functionally different compared to macrophage tropic strains derived from the immune system [46]. Similarly, the Tat protein of HIV also evolves in the brain and while it maintains its HIV activation properties [47], it may vary in its neurotoxic potential [48]. The brain-specific mutations in the nef gene results in efficient replication in macrophages [49]. Viral sequences derived from brain macrophages and astrocytes show compartmentalization suggesting cell specific evolution in the brain [50]. Viral sequencing shows that the meninges contain virus from both the brain and peripheral tissues suggesting that HIV migrates out of the brain, and the meninges are an important conduit for viral transport [51]. The effect of antiretroviral therapy on evolution of HIV in the brain is not well understood. Poor penetration of antiretrovirals across the blood brain barrier might result in low frequency of antiretroviral resistant sequences in the brain and hence cART might drive the compartmentalization of HIV in the brain. cART has been shown to induce a switch in HIV co-receptor usage from CCR5 to CXCR4 which appears later in the CNS compartment compared to the periphery [52]. Importantly, even in patients on antiretroviral drugs, maximal viral evolution occurs within brain tissues of individuals with dementia compared to without dementia [53].

Neurodiagnosis

The diagnosis of HAND is difficult and relies on recognition of the clinical syndrome and exclusion of alternative diagnoses, rather than on specific laboratory-based findings. With the effort to eliminate viral reservoirs especially in the brain, imaging techniques will be critical. Several methods are being devised such as developing ligands for positron emission

tomography using molecular probes, antibodies to the envelope protein, gp120 or antiviral drugs. However, the ability of the probes and antibodies to cross the blood brain barrier is limited and if viral loads are low such techniques may not be sensitive enough, hence further research along these lines is necessary.

Treatment

Current approach to use of antiretrovirals for treatment of HAND

There are two challenges in the treatment of HAND. First challenge is to prevent HIV viral replication in the brain. This step is limited by the poor penetrance of cART into the CNS. Macrophages, the primary target of HIV in the brain, require much higher concentrations of antiretrovirals for effective control of viral replication than that required by T lymphocytes [54]. Additionally, resistance mutations in the virus can differ between the CSF and plasma, contributing to the potential reservoir of viral replication in the CNS [55]. A CNS penetration-effectiveness (CPE) index recently has been proposed to guide the choice of antiretrovirals in patients with HAND. Each antiretroviral drug is given a score of 1 to 4 (4 = much above average CNS penetration, 3 = above average, 2 = average, 1 = below average), and the sum of the individual agents' scores in a combination regimen provides the CPE score for that regimen. Individual ART agents with scores of 4 include zidovudine, nevirapine, and indinavir/ritonavir [56].

Eradication of HIV reservoirs from brain

Several strategies are currently being pursued for systematic eradication of the virus. (i) To activate viral replication in the reservoirs in the presence of cART to prevent the virus from spreading to other cells. Viral proteins produced by these latent reservoirs will be recognized by the immune cells and reservoir would then be eliminated. Broadly, these include drugs that could modulate epigenetic changes such as histone deacetylase inhibitors or immune activation therapies [57]. A concern with this strategy is that activation and production of viral products in the brain could lead to an infiltration of cytotoxic T cells. Infiltration of activated lymphocytes in the brain could be injurious to neurons [58] leading to an encephalitis termed, CNS-immune reconstitution inflammatory syndrome [59]. Further, similar strategies have failed to eliminate other persistent CNS viral infections such as JC virus and herpes viruses [59]. However, there may be a window of opportunity for viral eradication via this strategy before it enters the brain. (ii) Immune ablation is also being used for elimination of the reservoirs. Due to the associated toxicity and immune suppression it is being used only in HIV-infected individuals with leukemia or lymphoma. This approach targets dividing cells hence brain cells that are terminally differentiated may not be eliminated. (iii) Another approach is to engineer HIV resistant stem cells by creating mutations in the chemokine receptor CCR5 [60]. However, HIV can enter cells using the CXCR4 chemokine receptor hence creating additional blocks for viral replication should be considered.

Methods for enhancing cART delivery to brain

The selectively permeable blood brain barrier interferes with bioavailability of cART in brain due to highly efficient drug efflux systems in the brain [61, 62]. However, a recent study showed that further intensification of antiviral therapy with raltegravir, an integrase inhibitor which achieves high CSF concentrations [63], did not reduce HIV RNA levels in CSF or intrathecal immunoactivation [64]. Owing to the importance of getting antiretroviral drugs into the brain, a number of novel methods for delivery across the BBB are being developed. These methods include disruption of the BBB, development of nanoparticles with increased BBB permeability, uptake by brain microvascular endothelial cells via adsorptive-mediated transcytosis and cell-mediated delivery [65]. BBB penetrance is

dependent on nanoparticle size, shape, and protein and lipid coatings [65]. These physical properties affect drug uptake, release and ingress across the barrier. Recent reports suggest that nanotechnology can improve the delivery of antiretroviral drugs across the BBB so as to affect bio-distribution and efficacy for HIV-1 disease in the brain. These nanoparticles are taken up by monocytes and sheltered within these cells as they are carried across the BBB. The drug is then released to act within the CNS. These cells make great candidates for cell-mediated drug delivery to the CNS. Other laboratories have conjugated nanoparticles with Tat, which has an affinity for nuclear transport mechanisms [66]. This results in a nanoparticle that has high CNS penetrability while still bypassing efflux transporters to prolong exposure within the CNS.

Failure of neuroprotective and anti-inflammatory therapies

Since HIV does not infect the neurons, but degeneration of the neurons and accompanying glial cell activation is a prominent neuropathological finding in patients with HIV encephalitis, it was thought that neuroprotective and anti-inflammatory strategies should be effective in halting or slowing the progression of HAND. However, despite several carefully conducted phase 2 studies that have targeted excitotoxic pathways, cytokines and chemokines, none has shown promising effects [67]. However, these failures are not unique to HAND; similar approaches have failed or shown very modest effects in other neurodegenerative diseases as well. One interpretation of this data might be that once the complex cascades of pathways and feedback loops have been initiated leading to neuronal injury, blocking single molecules or receptors is not going to be able to protect the neurons. Thus either a combination therapy targeting multiple pathways or addition of regenerative approaches may be needed.

Conclusion and Future Directions

It is imperative that a better understanding of the viral reservoir in the brain be achieved in the antiretroviral era. An estimate of the size of the viral reservoir in the brain in vivo will be important, since an immune attack against a large number of cells would be very detrimental. While eradication of viral reservoirs is a laudable goal, eliminating HIV from the CNS is extremely challenging and even if possible except for a select few, these measures are not going to be applicable for the vast majority of HIV infected individuals. Hence other measures are needed to prevent the progression of HAND. A focus on controlling the co-morbidities is needed, since they can have a major impact on HAND. Further characterization of neuropsychiatric manifestations of HIV infection particularly depression and psychosis as an underlying comorbidity of HIV infection and as a consequence of HIV infection is necessary. Host genetic factors that may predispose to such manifestations also need to be studied. While major advancements in development of antiretroviral drugs have been achieved, the next generation of drugs needs to target the Tat protein since it may be a critical factor that drives neuroinflammation in these individuals.

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Figure 1. Magnetic resonance imaging of the brain from a 56 yr old patient with advanced HIV dementia. (A) This FLAIR sequence shows diffuse periventricular white matter high signal intensity lesions. (B) This shows enlargement of the ventricles and cortical atrophy.

Figure 2.
Risk factors for HIV-associated neurocognitive disorders