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Host and Viral Factors Influencing the Pathogenesis of HIV-Associated Neurocognitive Disorders

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Abstract

The human immunodeficiency virus (HIV) invades the central nervous system early in the course of infection and establishes a protected viral reservoir. However, neurocognitive consequences of HIV infection, known collectively as HIV-associated neurocognitive disorders (HAND), develop in only a small portion of infected patients. The precise mechanisms of pathogenesis involved in HIV-induced central nervous system injury are still not completely understood. In particular, most theories of HAND pathogenesis cannot account for either the selective vulnerability of specific neuronal populations to HIV-induced neurodegeneration or why only a subset of patients develop clinically detectable nervous system disease. Epidemiological and virological studies have identified a variety of host and viral factors that are associated with increased risk of developing HAND. Some host factors that predispose HIV-infected patients to HAND overlap with those associated with Alzheimer's disease (AD), suggesting the possibility that common pathogenic mechanisms may participate in both diseases. Here, we will review reports of host and viral factors associated with HAND and place these studies in the context of the data employed to support current theories regarding the molecular and cellular mechanisms that lead to HIV-induced neurodegeneration with additional focus on mechanisms common to AD pathogenesis.

Keywords

HIV; HIV-associated neurocognitive disorders; Alzheimer's disease; inflammation; autophagy; synapto-dendritic degeneration

Introduction

Infection with the human immunodeficiency virus (HIV) can lead to a syndrome of neurological dysfunction currently termed HIV-associated neurocognitive disorders (HAND; Antinori et al. 2007; McArthur 2004). HAND is the most recent acronym used to describe this syndrome and is inclusive of all previous designations including HIV-associated dementia (HAD) as well as milder forms of HIV-associated cognitive impairment that did not meet criteria for HAD. In this review, we will therefore employ the term HAND to describe all HIV-associated neurocognitive impairment.

The prevalence of HAND was once estimated at 20% of the HIV-infected population (McArthur et al. 1999). With the advent of highly active antiretroviral therapy (HAART) for HIV infection, the incidence of HAND decreased (Sacktor et al. 2002). Unfortunately, it is not

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at all clear that HAART provides long-term protection from HAND. In recent years, the incidence of HAND as an AIDS-defining illness has actually increased (Dore et al. 2003), and recent studies have estimated that the prevalence of HAND is unchanged (Tozzi et al. 2005) or escalating (McArthur 2004), even in populations with extensive use of HAART. The proportion of new cases of HAND demonstrating a CD4 count greater than 200 is also increasing (Sacktor et al. 2001).

In conjunction with the epidemiological evidence that HAND may not be decreasing as much as other HIV-associated morbidities, there are additional factors suggesting that HAART may not provide sufficient protection to prevent the central nervous system (CNS) complications of HIV infection. While HAART may arrest neurocognitive impairment in some populations with HAND (Shanbhag et al. 2005), a subset of patients is susceptible to developing a leukoencephalopathy secondary to immune reconstitution in an HIV-infected CNS (Rackstraw et al. 2006). Chronic neuroinflammation is also present even in HAART-treated patients (Anthony et al. 2005). These findings suggest that HAART does not provide complete protection from HIV-induced inflammatory responses in the CNS and subsequent neurodegeneration. As a consequence, it is possible that the proportion of HIV-infected individuals who develop HAND will increase as improvements in control of peripheral HIV complications continue to extend life expectancy, resulting in higher numbers of HIV patients with HAND. Therefore, elucidation of the pathogenesis of HAND with the aim of identifying therapeutic targets for the prevention and treatment of this form of neurodegenerative disease is needed.

Unfortunately, it is extremely difficult to develop a clear understanding of the mechanisms contributing to HAND because the relevant human tissue cannot typically be studied in an ex vivo experimental paradigm such as those employed to decipher HIV-induced degeneration of circulating immune cells. Nevertheless, investigators seeking to understand the biology of HAND do have a number of tools at their disposal. Initially, autopsy studies revealed that HAND overlaps with a neuropathological entity that has been termed HIV encephalitis (HIVE). Cases of HIVE demonstrated several common features including evidence for HIV-infected leukocytes in the brain, the presence of monocyte-like syncytia (giant cells) called microglia nodules and macrophage infiltration. However, the presence and degree of HIVE does not completely explain the clinical syndrome of HAND (Masliah et al. 1997). Additional tools that can be employed to clarify HAND pathogenesis include epidemiological associations, prospective studies using neuropsychiatric measures, functional imaging studies, and experimental data acquired using cell culture and animal models of HAND. Through the use of these tools, a number of theories have emerged regarding the probable mechanisms that eventually lead to neuronal degeneration and/or neurological dysfunction. Most of these theories also attempt to explain why only a subset of the HIV-infected population are vulnerable to HAND. In the absence of the ability to perform definitive experiments, the consensus has developed that HAND develops secondary to a convergence of host and viral factors that contribute to determining which HIV-infected populations are at greatest risk. In this review, we will discuss the evidence for why several host and viral factors may contribute to HAND susceptibility and provide potential mechanistic explanations for how some of the host and virological features associated with HAND contribute to pathogenesis.

Host factors and the risk of developing HAND

Age-related factors

Antiretroviral therapy has led to long-term survival for HIV-infected individuals. Thus, the number of HIV-infected persons has increased along with the proportion of those who are considered “older” (over the age of 50; Goodkin et al. 2001). While the incidence of HAND has decreased since the introduction of HAART, the prevalence of HAND appears to be on

the rise (Dore et al. 2003; McArthur 2004). The accumulation over time of reversible or treatable environmental and host factors may contribute to the risk of developing HAND in those that continue to live with the disease over decades. Studies have begun to characterize cognitive changes in subsets of the population with HAND and reveal differences in the significance of risk factors between older and younger patients, suggesting that dementia in the aging HIV population may be a distinct entity from that of younger patients (Valcour et al. 2004b).

Epidemiological data from the Hawaii Aging with HIV cohort suggest that older age is associated with increased prevalence of HAND independent of duration of HIV-1 infection (Valcour et al. 2004b). Numerous studies have further supported the association between older age and increased risk of HAND (Chiesi et al. 1996; Janssen et al. 1992; Valcour et al. 2004a). Given the multiple clinical and pathological similarities discussed in this review between HAND and other age-related dementing illnesses, it is reasonable to speculate that host factors associated with dementia in the general population may also contribute to the observed increased risk of HAND in the older population.

Neuropathological similarities between HAND and Alzheimer's disease (AD), the canonical age-related dementia, include cortical neuronal loss and amyloid plaque deposition (Esiri et al. 1998; Everall et al. 1993; Green et al. 2005). Amyloid plaques in AD result from the deposition of amyloid beta (Aβ) which is a putative pathogenic molecule in AD. Aβ is the cleavage product of the amyloid precursor protein (APP) and APP mutations are associated with inherited forms of AD. The clinical implication or pathogenic consequences of Aβ deposition remains a debated issue in the AD field; however, the finding of Aβ deposition in both AD and HAND is suggestive of parallel pathways of chronic change that eventually result in cortical dysfunction characterized by the same "biomarkers". For example, decreased cerebrospinal fluid (CSF) Aβ and increased tau (a component of the neurofibrillary tangle, a second pathological hallmark of AD) have been suggested as sensitive and specific markers of AD in numerous studies (Galasko et al. 1998; Motter et al. 1995). It has recently been shown that changes in CSF Aβ and tau comparable to that seen in AD also develop in HAND patients (Brew et al. 2005). The pathogenic significance of these biomarkers is not well established. It has been hypothesized that decreased CSF Aβ reflects increased aggregation of insoluble Aβ and sequestration into amyloid plaques (Andreasen et al. 1999). However, decreased CSF Aβ levels have also been reported in neurodegenerative diseases not always associated with significant amyloid plaque deposition such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and prion disease (Formichi et al. 2008). Few studies have examined the correlation between CSF Aβ levels with plaque burden in AD and the results are conflicting. Methodological differences may have contributed to differences in outcome as one study measured Aβ levels from post-mortem ventricular CSF while another evaluated CSF from living patients (Engelborghs et al. 2007; Strozyk et al. 2003). Alternative hypotheses explaining decreased CSF Aβ in AD include neuronal degeneration resulting in decreased release of Aβ, epitope masking or formation of a high affinity complex between Aβ and CSF proteins in the pathological state (Otto et al. 2000). The cause of increased CSF tau is not known; it has been postulated to result from degradation of neurofibrillary tangles in dying neurons (Clark et al. 2003). Multiple studies have investigated how HIV infection may modulate Aβ generation and result in increased extracellular accumulation. The HIV protein Tat and Tat peptides have been shown to inhibit activity of neprilysin, a metalloendoprotease responsible for enzymatically degrading Aβ (Daily et al. 2006; Rempel and Pulliam 2005). Tat has also been shown to bind the lipoprotein receptor-related protein (LRP) and subsequently interfere with the uptake of LRP ligands including Aβ and apolipoprotein E (ApoE, also discussed below). These studies suggest that HIV infection may indeed have unique ways of perturbing the same molecular factors that contribute to neurodegeneration in AD.

ApoE, a lipoprotein important in lipid metabolism and transport, is expressed in three major isoforms ApoE2, ApoE3, and ApoE4, which are distinguished by variations at amino acid residues 112 and 158 (Poirier et al. 1993). The presence of the ApoE4 allele is a risk factor for the development of AD (Saunders et al. 1993) and may also be a significant host risk factor for HAND. While an earlier study found no correlation between the ApoE4 allele and the presence of dementia in HIV-infected patients (Dunlop et al. 1997), a cohort study following patients prospectively over a 5-year period reported increased diagnoses of dementia in ApoE4 individuals compared to ApoE4 negative controls (Corder et al. 1998). Disparate conclusions regarding the impact of ApoE may result from differences in study populations, or intriguingly, because ApoE4 may influence risk of HAND only in combination with increased age. For example, Valcour et al. reported that ApoE4 is a risk factor in the development of HAND only in the older population (Valcour et al. 2004b). Earlier studies may not have revealed the potential contribution of ApoE4 in the development of HAND because the study population was younger due to the discrete onset of the HIV epidemic and the later availability of life-prolonging HIV treatment.

Multiple mechanisms of ApoE modulation of neurodegeneration have been proposed and include lipid dysregulation, antioxidant action, degradation of Aβ, lipoprotein-mediated prevention of neuronal apoptosis, and modulation of astrocyte behavior (Cutler et al. 2004; Hayashi et al. 2007; Jiang et al. 2008; Kitagawa et al. 2002; van Meer et al. 2007). While this question remains unresolved, it is clear that some mechanisms of ApoE-mediated neuronal dysfunction might be shared between various neurodegenerative diseases. For example, chronic neuroinflammation is a well-established shared characteristic between HAND and AD (Smits et al. 2000). The innate immune response may be influenced by ApoE isoform as suggested by age-dependent increased expression of proinflammatory cytokines in ApoE4 transgenic mice (Harry et al. 2000). Microglia isolated from human ApoE4 transgenic mice also demonstrated a more proinflammatory phenotype compared to those expressing human ApoE3 (Vitek et al. 2009). Additionally, ApoE3 has been shown to protect against Tat neuronal toxicity while ApoE4 does not (Pocernich et al. 2004). Another mechanism by which ApoE may impact the risk for acquiring HAND is through directly impacting the dynamics of HIV infectivity. Recently, the ApoE4/E4 genotype was reported to be associated with more rapid HIV disease progression, and in vitro studies demonstrated that ApoE4 enhances HIV fusion and cell entry compared to ApoE3 (Burt et al. 2008).

Metabolism

Since its introduction in 1996, HAART has drastically improved the life expectancy of those living with HIV. The associated toxicity of long-term antiretroviral therapy includes the risk of developing central obesity, dyslipidemia, and insulin resistance (Behrens et al. 1999; Falutz 2007; Narciso et al. 2001) Thus, it is not surprising given the established association between these vascular risk factors and dementia, that long-term HAART use may actually contribute to the risk of acquiring HAND (Whitmer et al. 2005). However, independent of vascular CNS insults, these abnormalities, described collectively as “metabolic syndrome”, have also been associated with development of cognitive impairment. Central obesity has emerged a risk factor for dementia independent of the diabetes and cardiovascular co-morbidities (Whitmer et al. 2008). The role of diabetes and insulin resistance in the pathophysiology of dementia is being studied (Craft and Watson 2004), as epidemiological data have supported a role for impaired insulin response as a risk factor for dementia and AD (Arvanitakis et al. 2004) including patients without history of stroke (Biessels et al. 2006; Luchsinger et al. 2001; Valcour et al. 2006).

Another metabolic derangement observed in HAART-treated patients that might contribute to HAND risk is the effect of nucleoside reverse transcriptase inhibitors (NRTIs) on

mitochondria. HAART regimens that include NRTIs have been recognized as leading to mitochondrial toxicity and associated with cardiac, hepatic, hematologic, and myopathic morbidity (Lewis and Dalakas 1995; Lewis et al. 2003). Numerous mechanisms have been proposed to explain the deleterious impact of NRTIs including mitochondrial depletion, impaired mitochondrial replication via inhibition of the mitochondrial DNA polymerase gamma (POLγ), and subsequent increase in reactive oxygen species (ROS; Lewis et al. 2003). POLγ-independent mechanisms of impairing mitochondrial function have also been implicated, including decreased mitochondrial DNA transcription and altered expression of lipid metabolism genes (Mallon et al. 2005). Mitochondrial dysfunction is a feature of a number of neurodegenerative diseases including AD, Parkinson's disease, amyotrophic lateral sclerosis and Huntington's disease (Knott et al. 2008; Lin and Beal 2006). Oxidative damage can be identified early in the course of AD, suggesting ROS generation participates in the initial pathogenic events. AD models have shown that ROS promote increased Aβ production which subsequently may lead to further mitochondrial dysfunction (Lin and Beal 2006). Evidence for oxidative stress in the CNS has also been demonstrated in patients with HAND (Turchan et al. 2003). Proton magnetic resonance spectroscopy illustrates mitochondrial dysfunction in patients taking an NRTI as a component of HAART therapy. N-acetylaspartate levels, a marker of neuronal mitochondrial integrity, are lower in frontal white matter in HIV+ patients taking the NRTIs didanosine or stavudine compared to those who are HIV- or HIV+ on alternative ART (Schweinsburg et al. 2005). Additional evidence that NRTI exposure might cause neuronal injury by inducing mitochondrial toxicity comes from an investigation of synaptosomes and brain mitochondria treated with the NRTI, 2′, 3′-dideoxycytidine (ddC). In this study, ddC treatment led to cytochrome C release, decreased expression of the antiapoptotic molecule Bcl-2, and increased protein levels of the proapoptotic molecules caspase-3 and Bax (Opii et al. 2007), highlighting direct pathways between NRTI therapy and neuronal cell death and dysfunction.

Genetic predisposition

The variable course of disease progression in HIV-infected patients underscores the significant impact of host factors in HIV infection. Individuals infected for 10 to 30 years without measurable disease, are considered "long-term survivors". The identification of a subpopulation of long-term survivors suggested the possibility that host genetics influence HIV pathogenesis (Dean et al. 1996; Liu et al. 1996; Samson et al. 1996). Chemokines are small soluble ligands whose primary function is to signal the trafficking of leukocytes to sites of inflammation and injury and are categorized into distinct groups, labeled the CC, CXC, CX_3C, and XC chemokine families. Chemokine receptors, termed CCR or CXCR to denote "receptor", are transmembrane proteins which when bound to their soluble natural ligand, CCL or CXCL to denote "ligand", induce intracellular signaling pathways and subsequent leukocyte migration (Charo and Ransohoff 2006). HIV enters the cell via the CD4 molecule and the chemokine coreceptors, CCR5 and CXCR4, to invade monocytes and T cells, respectively. Macrophage targeted "M-tropic" virus may also use CCR2 and CCR3 for invasion (Reiche et al. 2007). These molecules were particularly interesting as candidate genes that may influence both HIV infectivity as well as the host response to infection. Clues to the etiology of variation in host resistance to HIV-1 were first uncovered with the discovery that a deletion polymorphism of CCR5 was associated with long-term survival (Dean et al. 1996). The CCR5Δ32 polymorphism, so named because it encodes a 32-base pair deletion in the coding region, resulted in a non-functional truncated protein (Liu et al. 1996). Multiple studies have confirmed the protective impact of CCR5Δ32 on HIV disease and have identified additional CCR5 polymorphisms that alter disease progression (O'Brien and Nelson 2004; Reiche et al. 2007). Similar clinical observations led to the related finding that genetic variants of CCL31, the highest affinity ligand for CCR5, also confer resistance to HIV infection. Copy number of a segmental duplication in the CCL31 gene is variable in the population, and those individuals

with a high CCL31 copy number are more resistant to HIV infection than those with a lower copy number (Gonzalez et al. 2005; Mackay 2005). While CCR5 and CCL31 are known to participate in the mediation of HIV entry, they also regulate cytokine release, chemotaxis, T-cell differentiation, and activation. Recent data suggest that variants in these molecules may influence HIV/AIDS pathogenesis independent of viral entry (Dolan et al. 2007). Likewise, the ligand for CXCR4 has been implicated through genetic studies to contribute to host variation in HIV disease course. Stromal-derived factor (SDF-1) also known as CXCL12 is the natural ligand for CXCR4 and the common polymorphism SDF1-3′A has been found to delay the onset of AIDS (Winkler et al. 1998).

The 2578G variant of CCL2 (MCP-1), is associated with increased CCL2 production and mononuclear phagocyte recruitment into infected or injured tissues. In the homozygous state, the -2578G CCL2 allele decreases the risk of acquiring HIV infection. However, in those infected, the -2578G allele is associated with more rapid disease progression and increased risk of HAND. This dichotomous response may be due to the proinflammatory properties associated with the allele, which may prevent initial microbial infection, but promote the deleterious effects of chronic inflammation in the CNS once infection is established (Gonzalez et al. 2002).

Candidate gene studies have also suggested possible roles for polymorphisms in the minor HIV-1 coreceptors CCR2 and, CX3CR1, and CCL5 (RANTES) associated with HIV disease progression (as reviewed in Reiche et al. 2007). CCR2, the CCL2 receptor, is not only a minor coreceptor for HIV-1 entry, but also an important mediator of microglia activity. CCR2 deficiency impairs microglia accumulation in a mouse model of AD leading to increased plaque accumulation and accelerated disease progression (El Khoury et al. 2007). Thus, polymorphisms in chemokine ligands and receptors may further impact disease acquisition and progression by mechanisms beyond viral entry.

Another candidate gene being studied is the inflammatory cytokine tumor necrosis factor alpha (TNFα). This proinflammatory cytokine has been implicated in mediating HAND pathogenesis in a large number of human studies and in vitro models of HIV neurological disease. Proinflammatory cytokines influence HIV-1 replication, and TNFα has been shown to increase HIV-1 replication possibly through induction of the transcription factor nuclear factor-kappaB (Fauci 1996). Elevated TNFα levels have been found in the CSF from patients with HIV dementia (Tyor et al. 1992) and relatively higher TNFα messenger RNA has been reported in HIV patients with dementia compared to HIV-positive patients without dementia (Wesselingh et al. 1993). The effects of increased proinflammatory cytokine release in neurodegeneration are well established. In addition to the more classically described deleterious effects of a cytotoxic milieu on neuron health, there may be specific pathways related to neurogenesis and neuronal precursor differentiation modulated by inflammatory cytokines released by monocytes in the CNS. For instance, human monocyte-derived macrophages infected with HIV induce neural cell precursor proliferation leading to increased gliogenesis and decreased neurogenesis (Peng et al. 2008). Several gene polymorphisms in the TNFα promoter have been identified that lead to increased TNFα production. The presence of a G to A change at position -308 (the “TNF2 allele”) has been associated with a number of human diseases (Louis et al. 1998), increased susceptibility to septic shock (Mira et al. 1999), and increased TNFα release in response to the bacterial endotoxin, lipopolysaccharide (LPS; Louis et al. 1998). The presence of TNF2 was found at higher frequency in HIV-infected individuals with clinically diagnosed dementia compared to those without (Quasney et al. 2001). A later study incorporating these data into a meta-analysis confirmed the increased association of the TNF2 variant in patients with HIV dementia compared to HIV-positive without dementia controls (Pemberton et al. 2008). Polymorphisms in the TNFα gene along with previously described variants in the interleukin-1β, IL1- RA, and ApoE genes had been examined by another group

where inclusion criteria was on a neuropathological basis though a definitive diagnosis of dementia was not known. In this study, the presence of neuropathological findings of HIV encephalitis such as microglial nodules, multinucleated giant cells, and myelin pallor was not associated with polymorphisms in the four genes studied (Diaz-Arrastia et al. 2004). Taken together, these data suggest that host genetic factors may specifically confer risk for the development of neurocognitive changes associated with HAND that is independent of the risk of developing end-stage neuropathological changes seen on autopsy. In summary, gene variants in inflammatory molecules may modulate neurodegenerative diseases such as AD and HAND in which neuroinflammation is a significant pathogenic process.

In addition to studying candidate genes that contribute to HIV pathogenesis, the field is now able to pursue genome-wide studies to perform unbiased searches for genetic variation associated with disease. One such study investigating samples from 30,000 patients of largely European origin identified single nucleotide polymorphisms (SNPs) that correlate to viral load and disease progression (Fellay et al. 2007). The HLA-B*5701 allele was one of two SNPs identified to correlate with viral load. This SNP had previously been postulated to associate with viral load through variable CD8+ T-cell response in the long-term survivors carrying the B*5701 allele (Migueles et al. 2000). Additional mechanisms by which HLA-B*5701 prevents HIV disease progression were hypothesized by the genome-wide association study authors to derive from its interaction with a SNP found in a nearby region, HCP5. Another SNP associated with decreased viral load was found near the HLA C gene. This SNP was associated with higher HLA C expression suggesting a potential mechanism for biological impact. Polymorphisms in a putative regulatory region of the ZNRD1 gene encoding an RNA polymerase subunit were associated with disease progression and also found to impact protein expression (Fellay et al. 2007). As with all genome-wide studies, replication of results and investigation in multiple populations will be required to clearly define these SNPs as important host risk factors. In addition, it has yet to be determined if any of these SNPs specifically impact the risk of acquiring HAND.

Environmental exposures and co-morbid conditions

The finding that many of the genetic risk factors associated with increased risk of HAND are in genes for factors that regulate or participate in inflammatory responses suggests that the type of inflammatory response mounted in the CNS by HIV-infected individuals may have a strong influence on whether or not CNS damage will develop. Additional support for this postulate can be found when noting other non-genetic factors that are associated with increased HAND risk. These include the risks associated with co-infection by additional pathogens and substance abuse.

Several of the practices that increase risk of acquiring HIV infection also lead to increased risk of infection by other pathogens. One such pathogen that is highly prevalent in populations participating in injection drug abuse is the hepatitis C virus (HCV). While HCV infection may produce some neuropsychiatric changes on its own (Laskus et al. 2005), several studies have demonstrated that the population co-infected with HIV and HCV have greater cognitive impairment (Cherner et al. 2005; Ryan et al. 2004). The association between HAND and HCV infection remains present in HAART-treated populations (Aronow et al. 2008; Tozzi et al. 2005) and appears to be independent of hepatic dysfunction secondary to HCV (Morgello et al. 2005). The mechanism by which HCV contributes to HAND is not well defined, but there is evidence to suggest that HCV does invade the brain where it may contribute to stimulate and/or exacerbate the neurotoxic inflammatory response believed to contribute to HAND pathogenesis (Laskus et al. 2005). Additionally, it has recently been reported that HAND is associated with higher systemic levels of plasma LPS (Ancuta et al. 2008). The hypothesis is that HIV-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. Interestingly, in the population studied, higher plasma LPS levels were associated with HCV infection as well as active intravenous heroin and/or ethanol abuse (Ancuta et al. 2008). Thus, it is possible that HCV infection may contribute to HAND risk via a common mechanism with substance abuse.

Intravenous drug use (IVDU) of several psychoactive substances including narcotics, methamphetamine, and cocaine has been hypothesized as increasing the risk of HAND. Studies have shown that even in the absence of AIDS, HIV-infected IVDU patients perform more poorly on neuropsychological tests (Ayuso-Mateos et al. 2000). Additionally, HIV-infected cases with a history of IVDU show more extensive evidence of microglia/macrophage activation in the CNS than patients with HIV infection and no history of IVDU (Arango et al. 2004). Whether these findings are explained by a direct effect of IVDU on systemic or CNS immune activation as suggested by the correlation with plasma LPS levels (Ancuta et al. 2008) or other secondary effects of drug and/or alcohol abuse such as nutritional deficiencies remains to be determined. For example, vitamin A deficiency, common among substance-abusing populations, may increase the morbidity and mortality of HIV infection via release from the antiinflammatory effects of retinoids (Royal et al. 2003).

In addition to IVDU, other forms of substance abuse may impact the neurocognitive outcome of HIV-infected patients. Methamphetamine abuse is associated with increased risk of neuropsychological impairment and both pathological and radiological evidence for neurodegeneration (Chana et al. 2006; Langford et al. 2003; Rippeth et al. 2004; Taylor et al. 2007). Experimental models of HIV-induced neuronal injury have suggested that methamphetamine interacts with HIV-Tat to induce synergistic neurotoxicity (Cass et al. 2003; Langford et al. 2004; Maragos et al. 2002). Alcohol abuse/dependence has also been suggested as a risk factor for HAND (Becker et al. 2004). However, population studies of the association between ethanol overuse and cognitive impairment in HIV infection have been conflicting (Nath et al. 2002), perhaps as a result of the inherent difficulties with identifying the specific level of ethanol intake that might lead to increased risk. In vitro experiments employed to directly relate alcohol toxicity as an exacerbating factor in HIV neuropathogenesis have implicated ethanol in disrupting blood-brain barrier (Shiu et al. 2007), as well as potentiating CNS injury caused by HIV-1 gp120 (Chen et al. 2005) and Tat (Self et al. 2004). In addition to the direct potential interactions between ethanol and HIV-1, the impact of chronic ethanol intake on CNS physiology as well as the peripheral immune system is established (Tyor and Middaugh 1999) and could contribute to HAND pathogenesis. Taken together, the experimental and epidemiological findings regarding the effect of methamphetamine or ethanol on HIV-induced neurotoxicity suggest that host factors such as substance abuse in combination with viral factors like sequence heterogeneity in Tat or gp120 may act in a concerted factor to result in neurodegeneration.

Viral factors that influence HAND risk

The HIV virus demonstrates extensive molecular genetic diversity in infected populations as well as in different tissue reservoirs within infected individuals. Thus, an early hypothesis regarding the pathogenesis of HAND was that viral genotype, and more specifically, the viral genotype resident in the CNS compartment, might have a determining impact on the likelihood of developing HAND. While data correlating the amount of viral replication within the CNS with detectable clinical disease remain controversial, there are nevertheless strong data in support of the hypothesis that viral genotype impacts HAND pathogenesis. These data come from studies aimed at determining the effect of viral subtype, or clade, as well as that of polymorphisms within specific viral genes on the likelihood of acquiring HAND or the ability of viral proteins to induce neurodegeneration.

Clade

HIV-1 has been classified into nine subtypes or clades labeled A-D, F-H, J, and K based on genetic diversity of the viral envelope (Sacktor et al. 2007). HIV-infected populations in Europe, the Americas, and Australia are predominantly infected with clade B HIV-1, while the remaining clades are generally distributed in Africa and Asia. Geographical differences in rates of HAND have been reported and hypothesized to reflect differences in the relative degree to which viral clades promote neuropathogenesis. However, reliable data on the rate of HAND in HIV-infected populations from resource poor countries are difficult to obtain and confounded by limited access to education and healthcare (Sacktor et al. 2007). When neuropsychological data from HIV-infected patients in Uganda were carefully compared to data obtained from a local control population, the rate of HIV-associated dementia was found to be similar to the rate of dementia in the USA during the days prior to the availability of HAART (Wong et al. 2007). Since HIV clades A and D predominate in Uganda, while most HIV in the USA is clade B, these findings suggest that viral clade may have little impact on HAND risk. However, in Ethiopia, where clade C is the dominant viral strain, HAND was much less prevalent than was observed in Uganda, suggesting that clade C HIV-1 is less likely to progress to HAND than other viral clades (Clifford et al. 2007). However, other studies of predominately clade C-infected populations in India and South Africa report HAND prevalence similar to that observed in populations where clade B dominates (Gupta et al. 2007; Modi et al. 2007).

Given the conflicting epidemiological and experimental data, it is difficult to determine at this point whether viral clade has an important influence on the risk of acquiring HAND as a complication of HIV infection. However, some data from HAND models suggest that the molecular variability in HIV strain may indeed be associated with differential neurotoxicity. One study using Tat molecules from clade B and clade C virus demonstrated that clade B Tat causes more neurotoxicity to cultured human neurons than clade C Tat (Mishra et al. 2008). It was also observed that when SCID mice were injected with HIV-infected human monocyte-derived macrophages infected with either clade B or clade C HIV strains, more neurotoxicity was observed in animals injected with clade C virus and that clade B virus was superior at inducing monocyte migration in a Tat-dependent manner (Rao et al. 2008). While it may seem difficult to reconcile the experimental and epidemiological data on HIV clade-specific neurotoxicity, it is quite possible that both are true. Since HIV subtypes occupy specific geographical niches, it is possible that while one viral strain may have more intrinsic neurotoxicity than another, differences in host factors may predominate in regional populations, resulting in similar HAND prevalence even when the predominant clade is less strongly associated with HAND.

Envelope

Though the data on HIV subtype association with HAND remain in question, there is additional evidence in support of the hypothesis that molecular variations within HIV can influence HAND pathogenesis. Perhaps the strongest evidence that viral heterogeneity is a factor involved in determining whether a particular individual will acquire HAND has come from studies of the viral envelope. Virus isolated from brains of demented and non-demented patients demonstrated specific clustering of envelope sequence variation in patients with dementia. Recombinant virus expressing envelope regions from demented patients elicited more indirect neurotoxicity than virus expressing envelop sequences derived from non-demented patients (Power et al. 1998). In addition, chimeric virus expressing envelope sequences derived from demented patients is more effective at inducing expression of proteins associated with the neurodegenerative inflammatory response (Johnston et al. 2000), suggesting a mechanism by which specific molecular features of the HIV envelope may contribute to neuropathogenesis in HAND. In another study, when brain-derived recombinant virus was expressed in cultured

macrophages, the culture media developed neurotoxicity that was independent of viral replication, dependent on envelope expression and could be blocked with anti-gp120 antibody (Zhang et al. 2003).

As these studies would predict, it has been observed that specific genetic variants in the HIV envelope are strongly associated with CNS tropism and risk of acquiring HAND. By isolating and sequencing HIV strains found more frequently in brains from HAND patients, Dunfee et al. identified the N283 variant in the CD4 binding site of HIV gp120 which may confer increased macrophage tropism and risk for dementia (Dunfee et al. 2006). Further support that HIV envelope sequence as a risk factor for HAND is suggested by a later study demonstrating that loss of the N-linked glycosylation site at D386 is also associated with HAND (Dunfee et al. 2007). It should be noted, however, that while specific molecular features of the HIV envelope are associated with increased risk of HAND, it is by no means clear whether or not this association is causal. In fact, it may well be that factors which impact host response may enable a greater degree of envelope evolution within each individual, which may secondarily predispose those infected individuals to acquire the most neurovirulent HIV variants. This was suggested by a study demonstrating suppressed serological neutralization of macrophage tropic virus in HAND patients compared to HIV-infected patients without dementia as well as greater envelope sequence diversity in the same group of patients with HIV dementia (van Marle et al. 2002).

Tat

The HIV Tat protein normally serves to regulate viral transcription, but has the unique feature of being able to traverse the plasma membrane of uninfected cells and translocate into the nucleus where it may impact host cell gene expression (van Marle and Power 2005). Numerous studies have demonstrated that HIV Tat has both in vitro and in vivo neurotoxicity (Huigen et al. 2004; van Marle and Power 2005). However, since the majority of these studies are done using the same recombinant form of Tat, these data cannot be used to support or refute the hypothesis that molecular diversity within the Tat sequence plays a role in acquiring HAND. Since Tat is secreted into the extracellular space, can enter uninfected cells, and has the function of inducing both viral and host gene expression (Huigen et al. 2004), it is quite possible that Tat sequence diversity might influence the degree and specificity with which Tat could impact gene expression in host cells. It has been demonstrated that brain-derived HIV strains demonstrate sequence heterogeneity specifically in regions related to the transactivation function of Tat (Mayne et al. 1998). An experiment aimed at examining the relevance of this diversity revealed that Tat sequences cloned specifically from brains of HAND patients were less capable at inducing transactivation of HIV transcription than Tat from non-demented patients, but did induce a specific pattern of host gene expression identified using microarrays (Boven et al. 2007). This finding suggests that while Tat sequence diversity may impact HAND pathogenesis, it is unlikely to be due to its role in activating viral gene expression. On the other hand, it seems quite possible that Tat variants would induce specific changes in host cell gene expression that may predispose patients infected by more neurovirulent HIV strains to develop gene expression changes that lead to neurodegeneration.

Other HIV genes

Several other regions of the HIV genome have been proposed to contribute to HAND pathogenesis. One example is the long terminal repeat (LTR) region. The LTR is involved in the regulation of viral gene expression via interactions with both viral and host-derived cis-acting transcription factors. The LTR contains two sites that bind to the CCAAT/enhancer binding protein (C/EBP) family of transcriptional regulators. Viral gene expression and replication in monocytes have been shown to require the C/EBP binding sites (Hogan et al. 2002). In one of the two C/EBP bindings sites within the HIV LTR, a specific sequence variant

(3T) has been associated with brain-derived viral DNA from patients with HAND (Hogan et al. 2003), suggesting that this important regulatory region for both viral gene expression and replication may be a key determinant of whether or not CNS HIV infection will result in a patient developing HAND.

Additional HIV genes encoding viral proteins also may contribute to HAND pathogenesis. For example, recombinant Nef protein is toxic to cultured neurons and promotes increased complement expression in astrocytes, which could then contribute to the innate inflammatory response to CNS HIV infection (Speth et al. 2002; Trillo-Pazos et al. 2000). Over-expression of Nef in astrocytes led to indirect neurotoxicity mediated at least in part by Nef-induced expression of the chemokine IP-10 (van Marle et al. 2004). However, viral diversity within the Nef gene did not differ between HIV/AIDS patients with or without dementia (van Marle and Power 2005). Thus, while the Nef protein may contribute to neuropathogenesis in combination with other viral and host factors, it is not clear whether molecular diversity of Nef genotype has a determining impact on neurovirulence.

The HIV Vpr protein may also play an important role in the neuropathogenesis of HAND, but little is known about whether Vpr sequence variation is important to the neurotoxic potential of this HIV gene. Extraviral Vpr is present in serum and CSF of AIDS patients and has been observed in CNS neurons and macrophages of tissue from patients with HIV encephalitis (Wheeler et al. 2006). Recombinant Vpr and Vpr-derived peptides exert significant neurotoxicity in models of HIV-induced neurodegeneration (Jones et al. 2007; Patel et al. 2000; Sabbah and Roques 2005). Vpr is a multifunctional protein capable of forming cation selective ion channels and recombinant extracellular Vpr can associate with neurons (Piller et al. 1998). Vpr is directly toxic to cultured neurons and transformed neuronal cell lines via modulation of currents and activation of apoptotic cascades (Jones et al. 2007; Patel et al. 2000; Piller et al. 1998; Sabbah and Roques 2005) and may also exert some indirect impacts on the function of astrocytes and microglia (Jones et al. 2007). Transgenic mice expressing Vpr in macrophage/microglia cells demonstrate apoptotic activation observed specifically in neurons as well as detectable behavioral deficits (Jones et al. 2007). Thus, Vpr maybe an influential viral factor involved in determining HAND pathogenesis, but more studies are needed to determine if specific viral genotypes of Vpr increase the risk of acquiring HAND.

A theory of HAND pathogenesis—overlaps with AD pathogenesis

Given the many variations in host and viral biology that seem to contribute to the risk of HIV-infected patients acquiring HAND, is it possible to develop a theory of pathogenesis that can include all of the documented associations? We believe that the majority of both host and viral factors associated with HAND are consistent with the theory of combined viral toxin and inflammatory mediator-induced neurodegeneration that has been espoused in a number of extensive reviews on HAND (Bell et al. 2006; Fischer-Smith and Rappaport 2005; Garden and Morrison 2005; Kaul and Lipton 2006; Nath et al. 2008). In this scheme, HIV enters the CNS via infected leukocytes soon after infection and resides in infected CNS leukocytes including perivascular macrophages and microglia (An et al. 1999). With time and diminished peripheral immune surveillance, viral replication in the CNS may reach a threshold where infected cells secrete viral proteins and inflammatory mediators that stimulate bystander cells to produce additional mediators of inflammation (Kaul et al. 2001). This process leads to the accumulation of inflammatory mediators (cytokines, chemokines, and proteases) as well as small molecules capable of stimulating excitatory amino acid receptors in the extracellular space and CSF (Cinque et al. 1998; Conant et al. 1999; Ferrarese et al. 2001; Gurwitz and Kloog 1997; Perrella et al. 1992). Multiple studies have demonstrated that specific inflammatory mediators elevated in brain and/or spinal fluid of HAND patients, such as TNFα (Wesselingh et al. 1997) and platelet activating factor (Gelbard et al. 1994) can lead to neuronal injury or loss. As would be

predicted by this theory of HAND pathogenesis, some of the specific identified genetic risk factors for HAND described above include polymorphisms in genes involved either in the recruitment of inflammatory cells to the CNS or in mediating the inflammatory response. CNS inflammation is also exacerbated by HCV infection (Bednarska et al. 2007) and drug or alcohol abuse (Anthony et al. 2008; Anthony et al. 2005; Flora et al. 2005; Tomlinson et al. 1999), a potential reason for why HCV infection and substance abuse are associated with an increased risk of HAND. In addition, as described above, several of the HIV proteins with known viral genotype-specific influence on the risk of HAND, including Tat, Nef, and gp120, have documented impact on bystander cells and promote neurotoxicity by modulating the inflammatory response. Thus, it appears that one unifying theme for many of the risk factors identified as increasing the likelihood of developing HAND is that they all lead to increased immune activation and inflammation within the CNS.

Alternatively, there are some host factors associated with increased HAND, such as age and ApoE genotype, which have not clearly been linked to CNS inflammation. Since both of these are also risk factors for the diagnosis of AD, this suggests that alternative cellular pathways associated with AD pathogenesis may also participate in the pathogenesis of HAND. For example, as in AD cases (Su et al. 1994) as well as mouse models of AD (Yang et al. 2008), the process of apoptosis has been shown to participate in neuronal loss. Patients with HAND also develop signs of apoptosis in a variety of CNS cell types (Shi et al. 1996). However, the activation of apoptotic mediators including p53 and caspase-3 is far more widespread than the number of apoptotic cells would imply (Garden et al. 2002, 2004; Jayadev et al. 2007). These observations suggested that molecular mediators of apoptosis might contribute to forms of subapoptotic neurodegeneration. Indeed, subapoptotic neural injury such as dendritic atrophy or loss of synapses and dendritic spines is more strongly associated with cognitive impairment in HIV patients than the number of lost or clearly apoptotic neurons (Masliah et al. 1997). Synapse and dendritic spine loss also correlate with cognitive impairment in AD (Terry et al. 1991) and are detectable prior to neuronal loss in animal models of AD (Jacobsen et al. 2006). Patients with the earliest clinically detectable form of AD, known as mild cognitive impairment also demonstrate synaptic degradation (Scheff et al. 2007). In a transgenic mouse model of AD with dendritic spine loss, the pathology was prevented by the ApoE2 genotype (Lanz et al. 2003), suggesting that this aspect of AD pathology is modified by ApoE genotype. Thus, it is possible that HAND-related synapse loss and dendrite degeneration are modified by risk factors that overlap with AD because the molecular mechanisms of synaptoxicity in both diseases also overlap. For example, both AD and HAND synapse loss have been suggested as regulated by overstimulation of glutamate receptors (reviewed in Kaul and Lipton 2006; Knobloch and Mansuy 2008) which then induce the activation of proteases that can disrupt the cytoskeleton and promote degradation of proteins involved in maintaining synaptic contacts. To test this hypothesis in a HAND model, we crossed mice with transgenic expression of a dominant negative caspase enzyme to the gp120 transgenic mouse model of HAND. We observed that inhibition of caspase enzyme activity prevented dendritic atrophy (Garden et al. 2002). This finding supported the hypothesis that apoptotic mediators contribute to clinically relevant neuropathology in HAND. Taken together, these findings suggest a mechanism by which ApoE genotype may predispose HIV-infected patients toward acquiring HAND if the genotypes that provide protection in AD prevent the synaptotoxicity induced either by inflammatory mediators and viral proteins in HAND or amyloid fibrils in AD. The precise molecular mechanism by which specific ApoE alleles impact the development of synaptic loss in either disease remains to be determined.

Yet another example of how AD and HAND pathophysiology may overlap comes from studies of a cell death mechanism known as autophagy. Autophagy is a process initially defined in yeast, whereby damaged cellular elements and misfolded proteins are targeted for specific and tightly controlled molecular pathways of degradations. Several investigators have identified

evidence for increased amount of autophagy in AD (Moreira et al. 2007; Nixon et al. 2005) and AD models (Boland et al. 2008; Yang et al. 2008) including evidence for autophagic vacuoles in dystrophic neurites (Boland et al. 2008). Recently, studies involving in vitro, rodent, and primate models of HAND have reported data suggesting that both proinflammatory cytokines and glutamate inhibit the process of autophagy which in turn promotes the activation of apoptotic mediators (Alirezaei et al. 2008). This finding was similar to a report using the PS1/APP transgenic mouse model of AD where enzymatic inhibition of a key regulator of autophagy leads to increased activation of neuronal caspase enzymes (Yang et al. 2008).

Taken together, these studies suggest a potential common pathogenic mechanism for synapto-dendritic degradation in HAND and AD. In this paradigm, the inflammatory responses induced by HIV or Aβ promote the accumulation of cytokines and excitatory amino acids that converge on neurons to prevent autophagy and promote the induction of proapoptotic proteolytic events that degrade neuronal connections. Thus, while the primary molecular pathology in both diseases is unique (HIV infection vs. the accumulation of Aβ) the downstream events that produce cognitive impairment may have important functional overlap. This would explain why several epidemiologically identified risk factors are shared between the two diseases.

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