Published in final edited form as:

Prog Neurobiol. 2010 June ; 91(2): 185–187. doi:10.1016/j.pneurobio.2009.10.016.

HIV and antiretroviral therapy: Impact on the central nervous system

Ronald Ellis, M.D. PhD

Summary

The HIV pandemic represents a major source of neurological morbidity worldwide. Emerging data from diverse populations indicate that HIV leads to significant neurocognitive impairments that reduce individuals' ability to contribute to the well being of their families and society. HIV affects vulnerable populations with many comorbidities, but the virus contributes to neurocognitive impairment independent of these conditions. The neuropathological substrate of HIV neurocognitive disorders is damage to synapses and dendrites, without major neuronal loss. This suggests the potential for substantial reversibility if synaptodendritic function can be restored. In the developed world, combination antiretroviral therapy (CART) leads to improved neurocognitive function as well as morbidity and mortality in HIV. CART is being used in increasing numbers of individuals in resource limited settings. New cases of severe dementia are now rare in populations where effective CART has been deployed. While some degree of neurocognitive improvement with CART is almost universal, many individuals do not achieve full restoration of their premorbid neurocognitive status, and milder degrees of impairment remain quite prevalent. Optimizing neurocognitive recovery is likely to require the development of better CNS penetrating antiretroviral regimens and the use of neuroprotective agents.

Introduction

At the end of 2007 there were approximately 33 million people living with HIV worldwide (UNAIDS, 2008). Across the globe HIV comprises a variety of major groups and subtypes, however, group M overwhelmingly predominates, and within this group subtypes B, C and A/E recombinants are the most prevalent subtypes. Viruses of a specific subtype are genetically more related to one another and often cluster in geographic regions because of founder effects. Whether subtypes differ from one another in their propensity to cause neurologic disease remains unclear. But the majority of research on HIV CNS disease has taken place in regions where subtype B is prevalent.

Systemic Pathogenesis

Human immunodeficiency virus type 1 (HIV-1) principally infects activated CD4+ lymphocytes, and secondarily infects cells of the monocyte-macrophage lineage, which then carry virus into the CNS. Acute infection may go unnoticed, as symptoms are quite nonspecific. What was once considered to be a period of clinical latency lasting many years

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Corresponding Author: Ron Ellis, MD, PhD, University of California, San Diego, 150 W. Washington St., San Diego, CA 92103 USA, roellis@ucsd.edu, Telephone: 619-543-5079, Fax: 619-543-4744.

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after acute infection is now recognized as a time of continuous high level viral replication and immune activation that leads to gradual depletion of CD4⁺ lymphocytes. The result is acquired immune deficiency syndrome (AIDS), which is characterized by susceptibility to various opportunistic infections.

Antiretroviral therapy

Combination antiretroviral therapy (CART; also known as highly active antiretroviral therapy, or HAART) has produced dramatic improvements in health and longevity for HIV-infected individuals. CART typically comprises at least three antiretroviral drugs from two or more different classes. Multiple drugs are needed to inhibit HIV replication at several stages in the viral life cycle, reducing the likelihood of drug resistance. Judicious use of antiretroviral therapy, by suppressing viral replication and partially restoring immune function, can prevent opportunistic infections and markedly prolong survival with HIV. As a result, most new cases of HIV brain disorders in the developed world today result not from opportunistic infections, but from primary HIV disease of the nervous system.

Neuropathogenesis

HIV is a neurotropic virus, reaching the central nervous system via trafficking macrophages early after initial infection. However, the virus does not infect neurons directly. Rather, productive infection in the CNS is sustained by tissue macrophages and microglia, and neurons are injured by indirect mechanisms, including virally encoded protein products such as gp120. Additionally, cellular activation in response to the infection produces downstream effects on neurons mediated by cytokines, chemokines and other immune mediators. Together these viral toxins and host mediators damage the elaborate network of connections between neurons - synapses and dendrites. Synaptodendritic injury in turn disrupts the highly integrated functioning of distributed neural systems, leading to HIV-associated neurocognitive disorders (HAND). The expression of neuroprotective and regenerative proteins is increased in HIV brains, reflecting compensatory repair processes. Because both viral and host factors play a role in HAND, effective treatment might require both CART and so-called “adjunctive” therapies that include neuroprotective and neuroregenerative agents.

Neurocognitive impairment in HIV

Although the neurocognitive impact of HIV in Western populations has received considerable attention, only recently has systematic research begun to appear on the larger HIV⁺ populations in Africa and Asia. There has been speculation that the neurocognitive disorders seen in Western populations may be attributable to comorbidities such as recreational drug use and other factors. However it is becoming clear from studies done in these other regions that neurocognitive impairments of similar type and degree affect HIV⁺ individuals despite the absence of these comorbidities. For example, Heaton et al. (2008) studied a unique population of rural inhabitants in China who acquired HIV parenterally through unsterilized biomedical equipment. Historically, a large number of poorly regulated commercial plasma collection companies operated in China, some using nonsterile techniques. Residents would supplement their small farming incomes by selling their plasma, in some cases very often, and many acquired HIV infection through this route. Researchers recruited 203 HIV⁺ and 198 HIV⁻ former plasma donors from rural Anhui province and performed detailed neurocognitive, medical and laboratory assessments. Participants were matched with respect to age and gender, and educational levels averaged 5–6 years in both groups. 87% of the HIV positive individuals took combination antiretroviral therapy. Many of the individuals in both groups were found to be seropositive for hepatitis C virus (HCV) as well. Among those without HCV infection, neurocognitive

impairment was significantly more prevalent in those with AIDS (38%) and HIV+ subjects without AIDS (27%) compared to HIV- individuals (13%). Although generally mild/moderate in degree, neurocognitive impairment had a substantial adverse impact on their lives, since those with impairment were significantly more likely to show disability in instrumental activities of daily living than those without impairment. HCV was associated with an additive adverse impact on neurocognitive function in co-infected individuals.

Impact of antiretroviral therapy in the developing world

In Western countries where combination antiretroviral therapy is widely available, treatment has greatly benefited the health of HIV+ individuals. Between 1995 and 1998, when protease inhibitor-based CART was introduced, death rates were cut more than 3 fold, and some opportunistic CNS diseases declined from 2–10 fold. Severe HIV dementia has become much less common, but recent studies have definitively shown that milder degrees of cognitive impairment persist. For example, the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study is a prospective neurological study of 1555 HIV+ individuals at 6 centers across the US (Heaton et al. 2009). Comprehensive neuromedical and neuropsychological (NP) evaluations were done on all subjects in this diverse cohort of men (77%) and women (23%) with a mean age and education of 43.2 years and 12.7 years, respectively. Forty-nine percent of subjects were African American, 9% were Hispanic, 39% were non-Hispanic whites and 3% were of other racial/ethnic backgrounds. Risk factors were IV drug use in 27% and men having sex with men in 58%. Seventy-seven percent took CART. Overall, 45% of the cohort met criteria for global neurocognitive impairment. Participants were classified according to severity of comorbidities - factors that might contribute to neurocognitive impairment independent of HIV, such as epilepsy (Antinori, et al. 2007). Impairment was common (39%) even among those on CART who did not have significant comorbidities. Thus a high prevalence of neurocognitive impairment was found in this large, geographically and demographically diverse HIV+ population despite the majority receiving CART.

The impact of this persistent neurocognitive impairment can be evaluated in several ways. First, impairment is associated with reduced employment and disability in activities of daily living. Additionally, it predicts an increased risk of late antiretroviral treatment failure and higher mortality despite CART (Tozzi et al. 2005). Researchers disagree on the sources of this persisting impairment. On one hand, it is possible that irreversible prior brain injury has occurred. Alternatively, because cart doesn't eradicate infection, inflammation in the CNS may continue to interfere with normal function. The failure of some antiretroviral drugs to reach the CNS also may contribute to persistent neurocognitive impairment by permitting smoldering follow replication in the CNS. There is strong evidence from observational studies of ARV regimens predicted to have greater CNS penetration yielded a higher proportion of patients with undetectable viral loads in cerebrospinal fluid (Letendre et al, 2008). Finally, improvements in neurocognitive performance after 12 weeks of HAART are greater among individuals who received antiretroviral regimens with better CNS penetration (Cysique et al. 2009).

Thus several key questions are raised by emerging observations concerning HIV CNS disease in the era of CART. First, does chronic infection of the CNS by HIV lead to irreversible neural injury? What is the full extent of neuronal recovery that may be expected with CART? Can this recovery be facilitated and further injury prevented? An ongoing, randomized clinical trial evaluating the potential effectiveness of a practical strategy for optimizing the CNS penetration of antiretroviral treatment regimens (May Et al. 2007) is expected to yield some answers to these questions.

Acknowledgments

Most of the research described here was performed in the context of the HIV Neurobehavioral Research Center at the University of California, San Diego. The HIV Neurobehavioral Research Center (HNRC) is supported by Center award MH 62512 from NIMH. The San Diego HIV Neurobehavioral Research Center (HNRC) group is affiliated with the University of California, San Diego, the Naval Hospital, San Diego, and the Veterans Affairs San Diego Healthcare System, and includes Director: Igor Grant, MD; Co-Directors: J. Hampton Atkinson, MD, Ronald J. Ellis, MD, PhD, and J. Allen McCutchan, MD; Center Manager: Thomas D. Marcotte, PhD; Heather Bentley, CCRA; Melanie Sherman; Naval Hospital San Diego: Braden R. Hale, MD, MPH (P.I.); Neuromedical Component: Ronald J. Ellis, MD, PhD (P.I.), J. Allen McCutchan, MD, Scott Letendre, MD, Edmund Capparelli, PharmD, Rachel Schrier, PhD; Jennifer Marquie-Beck; Terry Alexander, RN; Janis Durelle; Neurobehavioral Component: Robert K. Heaton, PhD (P.I.), Mariana Cherner, PhD, Steven Paul Woods, PsyD, David J. Moore, PhD; Matthew Dawson; Neuroimaging Component: Terry Jernigan, PhD (P.I.), Christine Fennema-Notestine, PhD, Sarah L. Archibald, MA, John Hesselink, MD, Jacopo Annese, PhD, Michael J. Taylor, PhD, Brian Schweinsburg, PhD; Neurobiology Component: Eliezer Masliah, MD (P.I.), Ian Everall, FRCPsych, FRCPATH, PhD, Cristian Achim, MD, PhD; Neurovirology Component: Douglas Richman, MD, (P.I.), David M. Smith, MD; International Component: J. Allen McCutchan, MD (P.I.); Developmental Component: Ian Everall, FRCPsych., FRCPATH., PhD (P.I.), Stuart Lipton, MD, PhD; Clinical Trials Component: J. Allen McCutchan, MD, J. Hampton Atkinson, MD, Ronald J. Ellis, MD, PhD, Scott Letendre, MD; Participant Accrual and Retention Unit: J. Hampton Atkinson, MD (P.I.), Rodney von Jaeger, MPH; Data Management Unit: Anthony C. Gamst, PhD (P.I.), Clint Cushman (Data Systems Manager), Daniel R. Masys, MD (Senior Consultant); Statistics Unit: Ian Abramson, PhD (P.I.), Florin Vaida, PhD, Christopher Ake, PhD. The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, nor the United States Government.

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