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HIV Associated Neurocognitive Disorder

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Abstract

Purpose of review—HIV associated neurocognitive disease (HAND) is the most active topic for neuroAIDS investigations at present. Although impairment is mild in patients successfully treated with modern antiviral regimens, it remains an ongoing problem for HIV patients. It is important to update the emerging research concerning HAND.

Recent findings—The virus enters the brain during acute infection, with evidence for abnormal functioning that may occur early and often persists. Direct relationships with ongoing viral infection continue to be monitored, but chronic inflammation, often associated with monocytes and macrophages appear to be the most likely driver of cognitive dysfunction. Appreciation for cerebrovascular disease as a significant co-morbidity that is associated with cognitive deficits is increasing. Neuroimaging is actively being developed to address detection and measurement of changes in the brain. Optimal cART therapy has vastly improved neurologic outcomes, but so far has not been demonstrated to reverse the remaining mild impairment. Inflammatory and vascular mechanisms of cerebral dysfunction may need to be addressed to achieve better outcomes.

Summary—Ongoing research is required to improve neurological outcomes for persons living with HIV. It is likely that interventions beyond antiviral approaches will be required to control or reverse HAND.

Keywords

HIV; HAND; neuroAIDS; neuroimaging; therapy

Introduction

Human immunodeficiency Virus (HIV) leads to neurologic conditions caused by opportunistic complications of immunodeficiency as well as the virus itself. Historically, the opportunistic infections occurring because of immunodeficiency were a substantial challenge. These are dealt with elsewhere in this issue, and are a declining proportion of neuroAIDS challenges because HIV is often treated early and effectively, limiting the pool of severely immunosuppressed patients. Thus, a majority of the research focus in the past

Conflicts of Interest

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year has been on the HIV-associated neurocognitive disorder (HAND). This problem has been primarily studied in resource rich regions, but almost certainly has global impact. In developing regions, the relative impact of co-morbidities on cognitive function likely is greater, but studies in multiple developing world sites suggest that HAND is important throughout the world. Challenges of measuring cognitive performance across social and cultural boundaries complicates interpretation, so the most incisive literature reviewed will report on HAND as it is presenting in the developed world.

Prevalence and Characteristics of HAND

Defining the prevalence of HAND remains controversial, and highly dependent on the populations studied and the techniques used. The leading methodology for defining HAND has been the Frascati criteria.[1] These classify HAND based on poor performance in at least two domains of neuropsychological (NP) function, and the degree to which daily functioning is impaired. In the absence of NP assessment prior to infection, along with the challenges of defining change in daily function, these criteria are challenging in research application, and impossible in most clinical practices. Recent evaluations suggest that they can also be used to detect dysfunction in the rapidly increasing group of HIV youth with HIV who also suffer cognitive impairment frequently.[2] In adults, the CHARTER cohort reports a high prevalence of HAND exceeding 50%, although many of these are asymptomatic or mild in the setting of available cART.[3] Co-morbidities such as drug abuse, co-infections, psychiatric challenges and prior injury contribute to particularly high burdens of HAND. While this prevalence has been found repeatedly in a variety of populations, it does not fully mesh with the experience of clinicians managing large numbers of HIV patients, who often are unimpressed with special cognitive problems. The possibility that diagnosis by Frascati criteria exaggerates the true HIV associated problem has been carefully re-addressed in the past few years in quite well designed and careful studies. Comparison of a stably combined antiretroviral treatment (cART) selected population with well-matched HIV uninfected controls, multivariate normative comparison was used to detect cognitive impairment. This careful analysis affirms worse performance in 17% HIV positive patients in domains of attention, information processing speed and executive function compared 5% of HIV negative controls who were impaired.[4] Further analysis affirms that decreased cognition in the HIV group is likely multifactorial with contributions from HIV-associated factors such as having experienced advanced immunodeficiency, but also cardiovascular/metabolic factors, drug use such as cannabis, and depressive symptoms. [5] This balanced view may help explain why therapeutic attention primarily to HIV itself has yielded little progress in eliminating residual deficits in HIV patients.

Determination if the cognitive impairment detected in HIV patients is progressive is important. The broad evidence of benefits of viral control with cART argue for treatment of all diagnosed HIV patients. Whether therapy can be optimized for the brain remains an open question, but it will be ethically challenging to study biology of HIV in the nervous system without cART. On therapy, if the lesions are fixed, and little progression occurs, trials to prevent progression are doomed to failure, unless they are neuro-restorative. Longitudinal studies are costly and complex, but some observations are now emerging. The CHARTER group has reported longitudinal analysis of its cohort showing a majority of patients do not

progress over a mean of 35 months observation, although a subset shows improvement while a slightly larger minority have worsening.[6] Analysis again suggests complex associations predicting changing function including HIV disease factors, but also non-HIV comorbidities and psychiatric conditions. The Multicenter AIDS Cohort has also reported a subset of patients studied longitudinally, and out of the third of patients determined to have impairment, 77% remained stable over ~4 years follow-up, with the remainder balanced between improvement and deterioration.[7] Interestingly, hypercholesterolemia was associated with progression, fitting with an emerging theme of the potential importance of vascular factors and HAND.

Acute Infection

A series of interesting observations regarding neurological status during acute infection have recently been reported. Many of these come from a prospective cohort of early infections studied by Serena Spudich and her collaborators in San Francisco, and a fascinating group of acute infections detected in Bangkok and extensively studied and monitored. Findings confirm early viral infection in the brain, often associated with neurological symptoms.[8,9] CNS inflammation increases, then is controlled by initiation of early therapy, surprisingly without evidence to date of neuronal injury.[10] These findings support emerging practices to start therapy as early as possible, and it will be important to follow the experience of these patients aggressively treated in the earliest days of infection. Limiting the pool of latently infected cells might have implications later on efforts to achieve a cure, and might change the degree of chronic inflammation that develops even on successful long term cART. However, the ultimate value of modulating early infection will be elusive. Many current patients doing very well lived long periods with advanced immunodeficiency, with remarkable restoration of health on initiation of antiviral therapy. However, earlier therapy seems likely to limit the latent pool of virus, and might avert the evolution of HIV virus to include macrophage tropic virus that is less CD4 receptor dependent characteristic of autonomous CNS infection.

Biomarkers and HAND

HAND has become difficult to study because it is most often asymptomatic or mild, and there are no sensitive and specific biomarkers to quantify and track its course. Some question the importance of an asymptomatic neurocognitive dysfunction, but concerns that this common complication cumulatively degrades the quality of life for many people, as well as portending possible greater dysfunction over time, make most researchers believe its importance is substantial. Ongoing efforts seek to give us better instruments that would be practical in busy clinics. The challenge is even greater when working globally across cultural differences, and potentially with different variants of virus.[11–13] Recent studies have evaluated several short performance tests including mini-medical state examination, International HIV dementia scale (IHDS), Montreal cognitive assessment, Simioni symptom questionnaire and cognitive assessment tool-rapid version (CAT-rapid) all compared with a standard full neuropsychological examination.[14,15] Such combinations as the IHDS and CAT-rapid performed well for detecting dementia, but no short testing was sensitive for the mild HAND that is the major clinical problem. Alternative neuropsychological assessments

seeking a pattern of deficits that would be more sensitive and specific is ongoing, with interesting observations that prospective memory (ability to remember to remember) might be a particularly informative focus.[16] A serious challenge for use of the Frascati criteria is how to detect and classify functional impairment. Commonly self-report is the only evidence used, but recent evaluations suggest that this is an insecure determination.[17] Given the serious lack of sensitivity of full neuropsychological batteries for HIV-associated deficits[18], the requirement that biomarkers with pathophysiological significance be found seems urgent.

Contribution of viral load measurement from CSF to diagnosis of HAND seems reasonable, and indeed viral escape with detectable HIV in CSF but not plasma is a real, but rare entity, that responds to changes in HIV therapy.[19] However, low level of HIV virus on very sensitive assays is often detected, and not clearly of diagnostic significance, although a recent report interestingly associates detectable CSF HIV with depressive symptoms.[20] It seems possible that detection of macrophage trophic virus in CSF suggesting adaptation of the virus for local replication might associate with cognitive dysfunction, as it does in untreated or unsuccessfully treated patients with dementia.[21] Monitoring evolution of HIV adapted to the CNS may become an important parameter detecting viral associated CNS inflammatory processes that might lead to impairment.[21,22] A potentially important viral related biomarker is detection of HIV DNA, particularly in circulating monocytes. Given the probable role of infected monocytes and microglia as the major HIV reservoir in the brain, correlation of HIV DNA in the circulation as a marker of increased risk of HAND appears reasonable and promising.[23,24]

The predominant hypothesis for ongoing dysfunction in the brain is that persistent inflammation is present even during cART therapy that impairs CNS function.[25,26] Systemic inflammation responds to cART, but not with resolution to normal, and ongoing macrophage/monocytic associated inflammation is characteristically resistant.[27] Since it is believed that CNS disease is likely driven by monocytic infection, markers of activation of these cells are promising targets for research, with some evidence associating plasma and CSF sCD163 to neuronal damage or impairment.[28–30] That markers of inflammation are present, and likely associated with impairment is increasingly evident, but proof that reversal of inflammation could be beneficial awaits future studies. Inflammation may be driven by microbial translocation with bacterial antigens leaking a through damaged GI tract to drive systemic and CNS inflammation. Evidence of sCD14 associated with elevated neopterin in untreated HIV patients is consistent with this, but the critical studies in treated patients with impairment have not been reported. [31] A recent report suggested that loss of CCR2 expressing monocytes was associated with cognitive impairment. This subset of monocytes inversely correlated with inflammatory activity reflected by CSF neopterin and plasma TNF. [32] While most of the literature has focused on monocyte associations with HAND, it is well recognized that activated lymphocytes can enter and leave the brain, and the contributions of CD8+ T cells producing interferon gamma have recently been associated with HAND as well.[33,34]

Monitoring the brain for neuronal damage by measurement of neurofilament light (NFL) in CSF has been a useful focus of recent research. Neurofilament light is detected as a result of

neuronal injury, with increasing levels found with advancing age and with evidence of CNS injury and dementia in untreated patients. Elevated NFL for age is sensitive to HIV associated injury and is elevated even in asymptomatic or mild HAND.[35,36] Recent use of high sensitivity assays for NFL in plasma allow replication of the pattern of NFL reflecting neurologic injury, while avoiding the use of lumbar puncture that limits assessments in many studies. [37]

Interest in the possible interaction of HAND and Alzheimer's disease (AD) as the HIV population ages has received considerable attention. APOE4 and aging are well described risks for AD and the impact of this genetic polymorphism in HIV has been assessed in a variety of settings. Analysis of CHARTER and MACS participants found no association of APOE status with development of cognitive impairment, or with imaging abnormalities in either structural or metabolic brain imaging.[38–40] A major reservation about these cohort analyses is the relatively young age, which might limit the power to detect APOE4 effects. In another recent report, while APOE4 was again not associated with HAND, it was associated with abnormal CSF- β 42 levels, consistent with increased risk of developing AD with further aging.[41] Remarkably, only recently was the first Alzheimer's disease in an HIV positive patient reported, suggesting that there is not a marked interaction of the pathophysiology of these conditions.[42] However, given the aging HIV population, and hoped for AD therapies on the horizon, it will become important to verify biomarker means to differentiate AD from HAND in the future. Indeed, it appears likely that CSF profiles and amyloid imaging developed for AD detection will be useful in differentiating these disorders.[43–45]

Traditional viral associated factors have in recent years appeared to diminish in importance compared to potential cardiovascular or metabolic risks for cognitive impairment in cART treated HIV. [46] Indeed, stroke risk is elevated in HIV patients suggesting that this population has more rapidly advancing vascular disease.[47] Diabetes with its known accelerated vascular disease is associated with earlier cognitive dysfunction.[48,49] Cohort studies continue to find substantial impact of cardiovascular associated factors affecting cognition, suggesting that this will be one of best areas of concentration to decrease cognitive impairment.[4,50]

Brain Imaging and HAND

Advances in brain imaging promise powerful ways to non-invasively assess the status of the brain over time in HIV infection, and may provide tools sensitive enough to employ as endpoints for clinical trials.[51] Given the limitations of neuropsychological testing, such alternatives may enable progress that has recently been stalled by lack of optimal endpoints for HAND. Structural MRI often reveals white matter changes of uncertain significance associated with HIV infection, but regional volumetric analysis can be a great tool to investigate progressive degeneration.[52] One of the very promising research imaging tools is PET scanning with ligands binding activated microglia that may be the effector cells for HAND. Early promising reports suggest this technology holds promise for HIV research. [53] Another rapidly expanding imaging approach is use of functional MRI by which circuitry underlying normal brain function can be mapped, with highly sensitive changes

observed associated with pathologic brain processes. HIV has already been shown to modify functional brain activity in multiple studies.[54–58] Measurement of brain perfusion also provides a sensitive measure of the health and activity of the brain which can now be measured with arterial spin labelling techniques using MRI. Magnetic resonance spectroscopy (MRS) has been applied to HAND for many years, and generally has shown evidence consistent with neuronal loss and persistent inflammation, but has not so far proved useful in diagnosis or management of HAND. [59,60]

Therapy

HIV therapy development has been a miraculous success story transforming a rapidly fatal disease to a chronic illness. HIV dementia is now vanishingly rare in patients receiving effective cART therapy, but ongoing investigations drill down on implications for the specifics of cART for the mild HAND still prevalent.[61] The hypothesis that smoldering HIV infection in the brain continues to drive HAND suggested that CNS penetration effectiveness (CPE) could be used to enhance therapy.[62] While this theory is attractive, the current implementation of it has not yet succeeded in predicting a means of enhanced therapy for HAND.[63,64] Indeed, the possibility that anti-retrovirals may be somewhat neurotoxic, and thus elevated levels in the brain could enhance HAND has been actively considered, although is also unproven at this point.[65,66] Efavirenz has received special attention for neurotoxicity due to the common neurologic sensations associated with its initiation and use. While efavirenz is a highly effective and generally well tolerated antiretroviral, there are ongoing concerns about its potential toxicity including both cognitive function and potential suicide.[67,68] However, functional connectivity analysis of HIV negative patients receiving efavirenz shows no evidence of neurotoxicity.[69] Efforts to improve treatment of HAND include intensification of therapy with more antiretrovirals, including CCR5 antagonists that some believe might be especially effective for the macrophage tropic virus in the brain. A recent pilot study of maraviroc supports ongoing larger trials to enhance therapy including such agents.[70] Similarly integrase inhibitors are very potent and should be active in the brain. Testing their impact with enhanced therapy is ongoing, but an early report of the impact of enhancing therapy in this way in acute infection failed to show benefit.[71]

Conclusion

HIV associated neurocognitive disorders represents an ongoing challenge to researchers interested in neuroAIDS. Evidence of active brain disease in otherwise successfully treated HIV patients suggests that the brain disease needs to be further investigated and understood to predict successful cure of HIV. Further, even mild cognitive dysfunction is likely to have serious cumulative effects on the quality of life, as well as the success of treatment for HIV. New molecular and imaging tools promise sensitive ways to probe the neurologic manifestations, and potentially to design informative studies that can move this field forward toward elimination of brain disorders from HIV.

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Key points

- HIV-associated neurocognitive impairment (HAND) is most often non-progressive in patients on cART
- Studies of acute infection affirm early infection of the brain and common acute neurological dysfunction or symptoms
- HAND deficits on treatment are generally subtle and difficult to verify with short, practical neuropsychometric tests
- Chronic inflammation is the most widely held mechanism hypothesized to cause HAND
- HAND is associated with activated monocytes and macrophages, with markers of these cells showing promise as disease markers
- Vascular disease and its typical associated markers appear important for HAND
- Neuroimaging has multiple modalities that are sensitive to changes of HAND and allow non-invasive monitoring of disease
- In absence of evidence for HIV activity driving HAND, attention to modifiable cardiovascular risks may be an alternative approach to therapy seeking to prevent or reverse HAND