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HIV, aging, and cognition: emerging issues.

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HIV, Aging, and Cognition: Emerging Issues

The prevalence of HIV-associated neurocognitive disorder has not changed from the pre– to the potent antiretroviral therapy era, remaining at approximately 50%. In research settings, mild neurocognitive disorder (MND) and so-called asymptomatic neurocognitive impairment (ANI) are now more common than HIV-associated dementia. The diagnosis of ANI is misleading because functional deficits, when tested in a laboratory, and degree of neuropsychologic testing abnormalities are often comparable in patients with ANI and those with symptomatic MND. Age-related comorbidities increase the risk of cognitive impairment in HIV infection. In a cohort of patients aged 60 years or older with excellent antiretroviral therapy adherence, correlates to cognitive impairment were apolipoprotein (Apo) E4 genotype and a novel measure of the effectiveness of antiretroviral drugs in monocytes, the monocyte efficacy (ME) score, with trend associations for diabetes and nadir CD4+ cell count. Management of impairment includes ensuring that patients are on and adhere to antiretroviral therapy and addressing comorbidities. Switching from effective and well-tolerated antiretroviral therapy for patients with mild cognitive impairment is not routinely recommended, but this must still be addressed on a case-by-case basis. This article summarizes a presentation by Victor G. Valcour, MD, at the IAS–USA continuing education program held in Atlanta, Georgia, in April 2013.

Keywords: *HIV, HIV-associated cognitive disorder, asymptomatic neurocognitive impairment, fluctuating cognitive impairment, progression, age-related factors, Alzheimer's disease*

HIV-associated neurocognitive disorder (HAND) reflects a spectrum of neurocognitive impairment. Mild neurocognitive disorder (MND) is defined by mild to moderate impairment in at least 2 cognitive domains on neuropsychologic testing and is typically associated with mild to moderate impairment of function. HIV-associated dementia (HAD) is defined by more severe impairment in at least 2 cognitive domains and is associated with more severe functional impairment. A third entity identified in the research setting is asymptomatic neurocognitive impairment (ANI), which is defined as any degree of neuropsychologic testing impairment in at least 2 cognitive domains but with no identified functional impairment. As discussed below, however, closer examination reveals that functional deficits can be identified in most ANI cases when tested in the laboratory.

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Characteristics of HAND

A comparison of data on cognitive diagnoses from the pre–antiretroviral therapy era with data acquired from the CHARTER (Central Nervous System [CNS] HIV Antiretroviral Therapy Effects Research) cohort in the current era indicates that there has been no change in the prevalence of cognitive impairment, with neuropsychologic testing impairment identified in approximately 50% of patients in both eras. It is estimated that the prevalence of HAD has decreased (from 18% to <5%), whereas there is an increased prevalence of mild symptomatic impairment (from 12% to 17%) and of ANI (from 20% to 28%).[1,2]

Some of the presentations of HAND may be missed by clinicians if they focus on pure memory impairment. Common cognitive symptoms observed include deficits in concentration, attention, and working memory, for example, the inability to juggle numerous tasks at the same time. Other cognitive symptoms include mental slowing and decreased comprehension. Motor components of the disorder may also be overlooked; these may include changes in gait, poor coordination, and tremor, with patients sometimes developing Parkinsonian features. Behavioral features commonly include apathy and depression but can also include agitation or mania. Although some of these behavioral features have been attributed to stress associated with having a chronic disease, imaging studies suggest anatomic correlates in a manner that supports a more direct contribution of HIV infection.[3]

Other data from the CHARTER cohort reinforce the fact that the probability of having a cognitive diagnosis is clearly associated with the presence of comorbidities in the form of confounding factors (Figure 1).[2,4] Confounding factors may include more overt factors such as drug use and less overt factors such as cerebrovascular disease. A high burden of white matter lesions on brain magnetic resonance imaging is often used as evidence for substantial small vessel ischemic disease, although HIV encephalitis can also cause white matter changes. In patients without confounding or contributing factors, the association of low CD4+ cell count and high plasma HIV RNA level with risk of cognitive diagnosis is more evident.

Determining an accurate incidence rate for cognitive impairment and particularly documenting progression in individual patients are hindered by fluctuation of impairment, which is common. A study comparing cognitive trajectories in HIV-infected and HIV-uninfected individuals showed that approximately 30% of HIV-infected patients changed cognitive status (improving, declining, or fluctuating) over time, a rate approximately twice

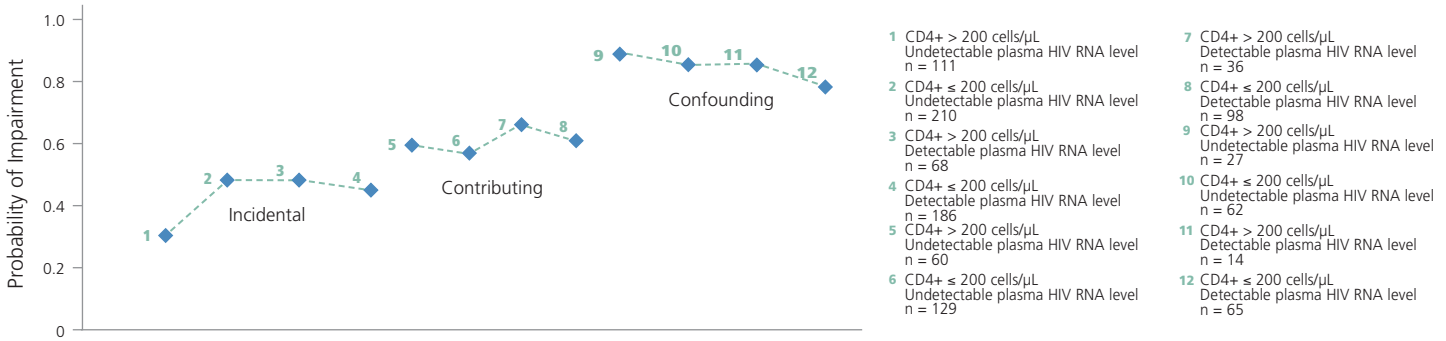

Figure 1. Probability of cognitive impairment by CD4+ cell count (below, at, or above 200 cells/μL) and plasma HIV RNA level (detectable or not) according to the presence of incidental, contributing, or confounding comorbidities. Adapted from Heaton et al.[4]

that seen for normal variation among HIV-uninfected controls.[5] Fluctuation of impairment is also suggested by findings in an ACTG (AIDS Clinical Trials Group) study reported by Robertson and colleagues. In this study, 21% of patients without cognitive impairment at baseline who either switched from failing antiretroviral therapy or started antiretroviral therapy exhibited testing performance in the impaired range after 48 weeks of treatment.[6]

It is important that clinicians convey to their patients that the course of cognitive impairment in HIV infection is typically not one of the relentless decline typical of neurodegenerative disorders such as Alzheimer's disease, which is supported by the fact that HAD remains relatively uncommon today. Thus, although many patients are afflicted by an irritating inefficiency in cognitive abilities, often affecting their quality of life and ability to perform typical work functions, progression to frank dementia is uncommon.

Asymptomatic Impairment

A recent study of more than 1500 community-dwelling HIV-infected persons with access to combination antiretroviral therapy, not all of whom had suppression of HIV RNA in plasma, showed that approximately 70% of those with nonconfounded HAND had ANI.[4] Although ANI might sound relatively innocuous, it may not be. It is commonly recognized that patients with cognitive disorders may not retain sufficient insight into their disease to self-report cognitive impairment. Yet, they are often the primary source of information about their cognitive symptoms as they come to clinical and research visits alone. Moreover, many are retired, on disability, or underemployed and may not have a complete understanding of whether they are functioning at their full cognitive potential. Further, cognitive changes may be insidious in onset, allowing for compensation without full awareness of these adjustments.

Neuropsychologic testing impairments have long been associated with functional impairment on tests of everyday functioning regardless of whether they are symptomatic or not.[7] A recent study involving neuropsychologic testing in persons aged 60 years or older in the University of California San Francisco (UCSF) HIV Over 60 Cohort showed no difference in degree of neuropsychologic testing impairment between HIV-infected individuals with ANI and those with symptomatic impairment (MND or HAD) (Figure 2, top).[8] In these same subjects and using a functional battery consisting of components for memory, judgment, driving (attention and executive function), bill paying (language and calculation), and map tasks (spatial ability), there was no difference in degree of impairment between the 2 groups (Figure 2, bottom).[8] Other studies similarly demonstrate problems with function related to employment capacity in subjects with ANI and those with MND.[9] Imaging studies from the UCSF HIV Over 60 Cohort also demonstrate broad areas of abnormal diffusion tensor imaging (DTI) suggestive of damage to white matter tracts.[10] In unpublished data from these same study participants, the DTI abnormalities correlate well with functional deficits regardless of whether subjects are symptomatic. Moreover, functional testing scores correlate to anatomic abnormalities, including the size of the corpus callosum, a major white matter structure in the brain.[11]

Individuals with ANI have a substantial risk of becoming symptomatic over time (Figure 3).[12] A major challenge in assessing and following cognitive function in asymptomatic and symptomatic impairment in HIV-infected individuals is the adequacy of proxy informants. In studies of patients aged 60 years or older at UCSF, patients are required to attend visits with a proxy informant or have one available via telephone. Although contacting informants for virtually all control and Alzheimer's disease subjects has been possible in this cohort, it has not been possible to reach 13% of informants for HIV subjects. Further, although approximately three-fourths of informants for control and Alzheimer's disease subjects live with the subjects, only 35% of HIV subject informants do so. Barriers to self-reporting are inherent among all subjects with cognitive disorders, but HIV patients may also have barriers stemming from stigma and other factors that may exacerbate the problem of acquiring accurate real-time assessments of functional capabilities.

Aging

By simply extrapolating data published by the Centers for Disease Control and

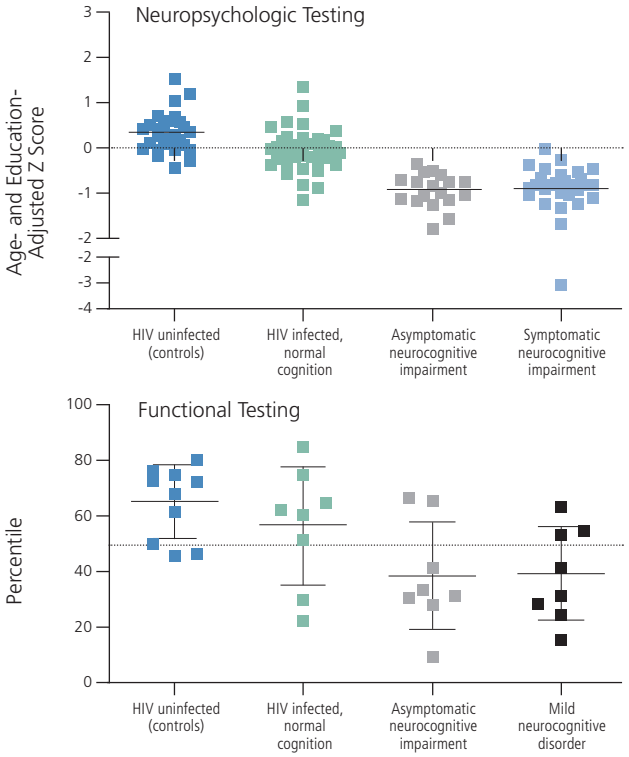

Figure 2. Similar deficits in patients with asymptomatic neurocognitive impairment (ANI) and symptomatic impairment on neuropsychologic testing performance (mild neurocognitive disorder [MND] and HIV-associated dementia combined) in the University of California San Francisco (UCSF) HIV Over 60 Cohort (top). Similar deficits on functional performance among patients with ANI and MND (bottom). Adapted from Chiao et al.[8]

Prevention (CDC), one can estimate that by 2017, 50% of HIV-infected individuals in the United States will be aged 50 years or older. The aging of the HIV-infected population, in association with effective antiretroviral therapy, might seem to be a phenomenon limited to developed countries, but this is not the case. In some areas of Africa, 5% to greater than 15% of individuals with HIV infection are older than 50 years.[13]

In the United States, most of the HIV-infected patients older than 50 years have been living with infection for a long time, with only approximately 11% acquiring infection after the age of 50 years. In the United States, many of these patients have polypharmacy and multimorbidity characterized by the interaction of comorbidities. By virtue of long-standing survival with HIV infection, often despite the death of their peers during a time when less optimal treatment options existed, these patients have characteristics of a survival cohort. This confounds the ability to understand risk factors for complications as this feature introduces heterogeneity. Although advancing age is consistently associated with declining cognitive performance in HIV infection, early data from the UCSF HIV Over 60 Cohort—ANI in 42%, MND in 53%, and HAD in 5%—do not appear to identify higher rates of impairment than rates published from younger populations.[11] Aside from survival influences, these rates may also be influenced by very high adherence to antiretroviral therapy and may thus differ from the younger CHARTER cohort.

In the UCSF HIV Over 60 Cohort, predictors of cognitive impairment consist of apolipoprotein (Apo) E4 genotype and the monocyte efficacy (ME) score, a novel measure of the effectiveness of antiretroviral drugs in monocytes,[14] with trend associations noted for diabetes and nadir CD4+ cell count. The ME score was recently defined to address the likely neuropathogenic mechanisms of infected monocytes trafficking virus to the brain as a substrate for cognitive impairment and appears to be independent of the CNS Penetration Effectiveness Score (CPE).[14,15] Factors not correlated with impairment include age (all patients were older than 60 years) and duration of HIV infection, current CD4+ cell count, plasma HIV RNA level (although most patients were fully suppressed), cardiovascular risk factors other than diabetes, and CPE score.

There is reason to be cautious about the utility of the CPE score in predicting outcomes or modifying approaches to antiretroviral therapy. Although limited by enrollment challenges, 2 randomized studies evaluated intensification of antiretroviral therapy based on CPE and neither supported the efficacy of this strategy.[16,17] One of these studies found worse outcomes with intensification for higher CPE. Findings such as these should lead to some skepticism with regard to changing regimens in patients with chronic, although possibly fluctuating, impairment. Currently, there are no data to support such a strategy as a means of preventing cognitive impairment. One must also consider that such strategies may, in fact, cause harm in patients who are otherwise tolerating or doing well on their existing regimen as it could expose them to new toxicities or impact adherence.

However, it is important to recognize that there have been clear cases of CNS escape, a phenomenon whereby HIV RNA is detectable in cerebrospinal fluid (CSF) when it is below the level of detection in plasma.[18] Such escape with concurrent clinical consequences seems to be relatively rare. Nevertheless, it complicates the approach to the evaluation of patients with cognitive disorders in HIV infection and necessitates a case-by-case evaluation.

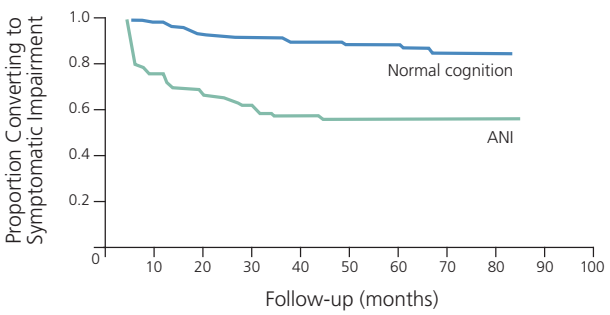

Figure 3. Conversion to symptomatic impairment over time in 347 patients with asymptomatic neurocognitive impairment (ANI) or normal findings on neuropsychologic testing in the CHARTER (Central Nervous System HIV Antiretroviral Therapy Effects Research) cohort. Adapted with permission from Grant et al.[12]

Are HIV-Infected Patients at Risk for Early Alzheimer's Disease?

It is not yet known whether HIV-infected persons are at risk for early Alzheimer's disease or a course of disease that is more aggressive. Many factors are at play in older patients that can contribute to cumulative brain damage and the clinical presentation of cognitive, behavioral, and motor disorders, including such potential age-related factors as neurodegenerative disorders, chronic immune activation, cumulative cerebrovascular comorbidities, and chronic exposure to antiretroviral agents. Studies have shown that amyloid burden in the brain increases with duration of HIV infection and appears greater among patients receiving antiretroviral therapy than in patients treated prior to the potent antiretroviral therapy era.[19,20] Although these findings are worrisome, the characteristics of these amyloid changes are not typical of the neuritic plaques seen in Alzheimer's disease.

More recently, novel brain imaging techniques have been used to investigate amyloid burden. One study using the Pittsburgh Compound B (PiB) amyloid biomarker noted no increase in amyloid among predominantly younger and cognitively normal HIV-infected subjects, whereas another study noted changes in CSF biomarkers that mimicked some characteristics of Alzheimer's disease patients.[21,22] Data from another, very small study have suggested that HIV-infected subjects with cognitive impairment have somewhat elevated brain amyloid compared with HIV-infected subjects without impairment, but this work requires confirmation in larger studies.[23]

Reports on the role of Apo E4, an Alzheimer's disease risk factor, in HIV have been mixed, and Apo E4 appears to be more relevant in older age.[24] After adjustment for CD4+ cell count, nadir CD4+ count, duration of HIV infection, and plasma HIV RNA level, patients positive for Apo E4 in the UCSF Over 60 Cohort had substantially greater deficits in global, psychomotor, and executive functions on neuropsychologic testing (Figure 4).[25] Although such findings suggest that cognitive impairment in HIV infection may share some pathways with Alzheimer's disease, it should be noted that the presence of Apo E4 has also been associated with poorer outcomes in a variety of cases, including cognitive problems associated with head injury.

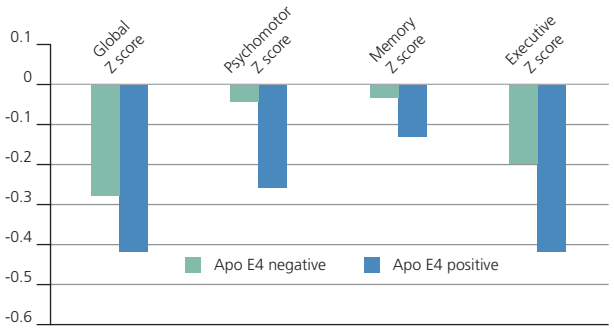

Figure 4. Association of apolipoprotein (Apo) E4 with poorer neuropsychologic testing performance shown by Z scores in patients in the University of California San Francisco (UCSF) HIV Over 60 Cohort (adjusted for CD4+ cell count, nadir CD4+ cell count, years HIV seropositive, and plasma HIV RNA level). Adapted with permission from Atputhasingam et al.[25]

Conclusions

HAND remains frequent despite the use of antiretroviral therapy. Asymptomatic cognitive impairment may not in fact be silent. Comorbid illnesses are important contributors to impairment, particularly in older age. To date, there are insufficient data to determine whether older HIV-infected patients are at increased risk of Alzheimer's disease.

The single most important intervention in managing cognitive impairment remains to ensure that patients are on antiretroviral therapy and are adherent to treatment, with suppression of HIV RNA in plasma. In patients not on treatment, the presence of cognitive impairment indicates that antiretroviral therapy is necessary. In most cases of cognitive impairment, there are insufficient data to support a standard empiric change in antiretroviral therapy if the current regimen is tolerated and plasma HIV RNA is maximally suppressed. However, cases of CNS escape have been described, necessitating an elevated index of suspicion and case-by-case management. In particular cases, lumbar puncture may be used to determine whether HIV RNA is detectable in cerebrospinal fluid, and in these cases, changing the antiretroviral therapy regimen to target this discordance is required. In addition, it is crucial to address comorbidities in patients with impairment, including drug or alcohol use, depression, and cerebrovascular risk factors.

At present, there are insufficient data to support the use of medications indicated for Alzheimer's disease, such as acetylcholinesterase inhibitors. One study failed to identify benefit for memantine, another drug approved for use in Alzheimer's disease.[26]

Exercise is a reasonable recommendation for all HIV-infected patients based on knowledge evidencing benefit for cognitive disorders in HIV-uninfected patients.[27] It can be beneficial for the psyche, helps with depression, gets people out of the house, and may reduce cerebrovascular risk factors. Cognitive stimulation may also have a role. Activities that patients find enjoyable, such as taking a course, learning something new, and being involved in an active social environment, are an easy way to introduce this and may provide a great deal of cognitive stimulation. Information on the potential benefits of formal cognitive stimulation exercises is emerging. Head-to-head comparisons of engaging in computer-based formal activities versus stimulating daily life activities are needed.

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