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Evolving clinical phenotypes in HIV-associated neurocognitive disorders

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Abstract

Purpose of review—This review describes changes in the presentation of HIV Associated Neurocognitive Disorders (HAND) comparing the current combination antiretroviral therapy (cART) treatment era, to the pre-cART era.

Recent findings—The frequency of the most severe stage of HAND, HIV dementia (HAD) has decreased, but the frequencies of milder stages of HAND, asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND), have increased. In the pre-cART era, HAD was a progressive disorder leading to death within months. With cART HIV+ individuals with HAND frequently remain stable over many years, though they may still show signs of ongoing central nervous system (CNS) injury. On neuropsychological testing, there may be a shift from prominent slowed motor and speed of processing deficits in the pre-cART era to a greater impact on learning, memory, and executive functioning deficits in the cART era. Importantly, ANI has recently been shown to lead to a 2 to 5 fold increased progression to symptomatic HAND. Thus, early recognition and treatment of those with ANI is important to protect the CNS over the long term.

Summary—HAND continues to be an important neurological manifestation in both HIV+ individuals naïve to cART and on cART.

Keywords

HIV; dementia; neurocognitive disorder

Introduction

In 2007, a revision to the existing diagnostic nomenclature and an algorithm was proposed by a working group sponsored by the National Institute of Mental Health and National Institute of Neurological Disorders and Stroke to define HIV Associated Neurocognitive Disorders (HAND) (1). The 2007 algorithm was an update from a previous nomenclature developed by the AIDS Task Force of American Academy of Neurology. The 2007 HAND

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algorithm defines three stages of increasing severity of cognitive impairment associated with HIV infection: 1) HIV-associated asymptomatic neurocognitive impairment (ANI), 2) HIV-associated mild neurocognitive disorder (MND), and 3) HIV-associate dementia (HAD). An important modification from the 1991 criteria was the addition in the 2007 algorithm of the ANI category to described HIV-seropositive (HIV+) individuals with cognitive impairment defined by formal neuropsychological testing but without any impairment in everyday functional tasks. HAND is defined by clinical assessments of both neurocognitive performance and functional performance. Neuroimaging and laboratory tests are used to exclude confounding conditions. This review describes changes in the clinical presentation of HAND with the introduction of combination antiretroviral therapy (cART) in 1996.

Temporal progression of HAND

There have been significant changes in the temporal progression of HAND. The frequency of the most severe stage of HAND, HAD has decreased, but the frequencies of milder stages of HAND, ANI and MND, have increased. In the pre-cART era, HAD was a progressive disorder leading to death within months. With cART the majority of HIV+ individuals with HAND remain stable over many years.

A subset of individuals may show clinical progression in their HAND stage. Some HIV+ individuals on cART may demonstrate ongoing CNS changes as identified by subcortical atrophy on neuroimaging or cerebrospinal fluid (CSF) measures of axonal injury such as elevated neurofilament protein levels in the absence of clinical changes (2), (3). Other HIV+ individuals may show clinical deterioration (2). Other HIV+ individuals may show clinical improvement which is sustained. Additional HIV+ individuals with HAND may have a fluctuating course from abnormal to normal and then abnormal neurocognitive performance again (1).

Impact of aging on HAND

By 2015, it is anticipated that 50% of HIV+ individuals will be > age 50 years (4–6). More than 75% of HIV individuals over 50 now die from non-HIV related causes (5) suggesting that the causes of cognitive impairment among older HIV+ individuals may overlap with those among elderly HIV- individuals such as cerebrovascular disease or neurodegenerative diseases. The aging of the HIV+ population may lead to changes in the neuropsychological test profile of HAND. Indeed, one study comparing the neuropsychological testing of HIV+ individuals > age 50 years to HIV+ individuals <age 50 years suggests a higher proportion of amnestic cognitive impairment among the older subjects compared to the younger subjects with HIV infection (7). The prevalence of motor signs of Parkinsonism such as bradykinesia and tremor is currently less in HIV+ individuals on cART compared to the pre-cART era, although with an aging HIV+ population, this reduction in motor symptoms may lessen.

Frequency of neurocognitive impairment and impact of comorbidities

As noted above and recognized by researchers and clinicians alike, there is a reduction in the severity of neurological and neurocognitive deficits associated with HIV after the

introduction of cART. Dramatic downward shifts in the incidence of HAD were evident, although increased longevity led to an overall increased prevalence of this more severe form of HAND (8). Recently published results on cohorts continue to find increased neurocognitive impairment prevalence rates in those on cART and suppressed systemic viral load as previously found in 2007 (9),(10). In the CHARTER baseline study (11), approximately 30% continue to have neurocognitive impairment in those who were suppressed with CD4+ counts > 200, and without substantial comorbidities. In HIV+ individuals with contributing co-morbidities, irrespective of CD4 lymphocyte count and viral load suppression, approximately 60% have neurocognitive impairment, and in HIV+ individuals with confounding co-morbidities, irrespective of CD4 lymphocyte count and viral load suppression, approximately 80% have neurocognitive impairment.

Changes in the neuropsychological test profile of HAND

Prior studies have demonstrated a change in the pattern of neurocognitive impairments along with the shift in the severity of deficits. An early study in this area combining two cohorts, monotherapy versus combination therapy, documented a shift to deficits in the learning domain from pre to post cART eras (12). A later study from the CHARTER and HNRC groups (13), found that in medically asymptomatic HIV+ individuals cognitive impairment was more common in a cART (2000–2007, n=937) sample compared to a pre-cART (1988–1995:n=857) sample. There was a shift from prior slowed motor and speed of processing deficits in the pre-cART era to an impact on learning, memory, and executive functioning in the cART era. Recent studies, have also confirmed a shift in the pattern of deficits from prior motor and speed deficits often associated with a subcortical white matter focus to more cortical/frontal deficits in learning, memory, and executive functioning.

Significance of the asymptomatic neurocognitive impairment stage of HAND

With the shift from the more severe impairments of HAD to the predominance of milder forms of HAND, there has also been a shift in clinical and research focus on ameliorating these milder forms and protecting the CNS for what is now a chronic disease in many living with HIV. Asymptomatic neurocognitive impairment (ANI) continues to be a compelling diagnostic category in HAND. Some researchers believe that the prevalence of HIV-related cognitive impairment is currently being overestimated through the use of neurocognitive assessment (14). However, biomarker studies demonstrate that there is neuronal injury in those who are neuroasymptomatic with HIV infection (15). Multiple studies have also demonstrated that neurological injury can occur early in HIV disease (3). A milestone publication from the CHARTER group recently demonstrated that those with ANI are 2 to 5 times more likely to progress to symptomatic neurocognitive impairment (16). This demonstrates the need for effective early identification and treatment of those who are not already on ART, and the potential need to screen for any other treatable causes of neurocognitive impairment (17).

Impact of CNS penetration of cART for the treatment of HAND

Treatment of HAND is predominantly with cART. Some antiretroviral drugs may have better penetration into the CNS than other antiretroviral drugs, but it is unclear whether a combination of antiretroviral drugs with better penetration into the CNS has a beneficial impact on neurocognitive performance. One study suggests that cART with better CNS penetration is associated with improved CSF HIV viral suppression compared to cART with less CNS penetration (18). However, a recent randomized trial of HIV+ individuals with HAND treated with a CNS-targeted cART with good CNS penetration compared to a non-CNS targeted cART with poor penetration showed no benefit in neurocognitive performance for the CNS-targeted cART arm (19). In addition, a recent large study of 61,938 HIV+ individuals followed for 37 months found that initiation of cART with better CNS penetration increased the risk of HIV dementia, suggesting a potential deleterious effect from cART with better CNS penetration (20).

HAND in international settings

As studies in resource-limited countries expand, HAND increasingly is being recognized as a neurological complication of HIV infection in international settings. Almost 70% of the world's HIV population resides in Sub-Saharan Africa where people are infected not with HIV subtype B which is predominant in North America but rather HIV subtypes C, A, and D. Initial studies where HIV subtypes A and D are predominant suggest that the overall frequency of HAD is high (31%) in untreated HIV+ individuals (21), but this frequency of dementia resembles the overall frequency of HAD in pre-cART cohorts in North America. If this frequency of HAD is seen throughout Sub-Saharan Africa and other resource-limited countries, then HAD may be along with Alzheimer's disease and vascular dementia among the top three causes of dementia globally. However, unlike Alzheimer's disease and vascular dementia, HAD is potentially reversible if it can be identified early, and cART can be initiated. The pattern of deficits in Uganda includes psychomotor slowing, executive dysfunction, and verbal memory deficits and is similar to the profile seen in US studies (22). Results of the neuropsychological profile from regions in Africa where HIV subtype C is predominant, *e.g.,* South Africa shows similar results (23). Additional studies are needed to determine whether specific HIV subtypes are associated with either an increased or decreased frequency of HAND.

Conclusion

In conclusion, HAND continues to be an important neurological manifestation in both HIV+ individuals naïve to cART and on cART. Future studies will determine to what degree age-related co-morbid conditions, such as vascular disease or neurodegenerative conditions including Alzheimer's disease, will contribute to the cognitive impairment in HIV+ individuals on cART who survive longer and advance in age.

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* Of special interest

** Of outstanding interest

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Key Points

- The frequency of the most severe stage of HIV associated neurocognitive disorder (HAND), HIV dementia (HAD) has decreased, but the frequencies of milder stages of HAND, asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND), have increased.
- With combination antiretroviral therapy, the majority of HIV+ individuals with HAND remain stable over many years.
- The aging of the HIV+ population may lead to changes in the neuropsychological test profile of HAND.