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Changing Clinical Phenotypes of HIV-Associated Neurocognitive Disorders

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Abstract

HIV-associated neurocognitive disorders (HAND) remains a common cause of cognitive impairment and persists in 15–55% of HIV+ individuals in the CART era. Combination antiretroviral therapy (CART) is now the primary treatment for HAND, but it is effective in only a subset of patients. In the pre-CART era, HIV-associated dementia was the most common form of HAND. However, in CART-treated patients the prevalence of HIV-associated dementia has declined substantially, and milder stages of HAND, *i.e.*, ANI and MND predominate. HIV+ patients with mild neurocognitive disorder (MND) can still have significant functional impairment in some activities of daily living. There have been several other significant changes in the clinical features of HAND in the CART era. The mean survival for an individual diagnosed with HIV dementia has increased dramatically. In HIV+ individuals on CART with a suppressed systemic viral load, the majority of individuals with HAND remain stable, with a small proportion showing deterioration. Extrapyramidal signs are now less common in patients with HAND on CART. In the CART era, HAND may have a mixed pattern of both cortical and subcortical features with greater deficits in executive functioning and working memory. Despite the milder clinical phenotype, in the CART era, patients with HAND still have persistent laboratory and neuroimaging abnormalities in the central nervous system even with systemic viral suppression. As the HIV+ patient population ages, cerebrovascular disease risk factors such as hypertension, diabetes, and hypercholesterolemia are increasingly recognized as risk factors for cognitive impairment in HIV+ patients on CART. HAND remains a common neurological condition globally in the CART era, necessitating the need for new animal models to examine pathogenesis and potential treatments for HAND.

Keywords

HIV; dementia; cognitive disorder

In the past 20 years, there have been several advancements in the treatment of human immunodeficiency virus (HIV) infection. Combination antiretroviral therapy (CART), introduced in 1996, can provide effective systemic suppression of HIV replication (1). The

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introduction of CART has resulted in a 50% decline in mortality rates associated with HIV infection, and CART has reduced the incidence of opportunistic infections associated with acquired immunodeficiency syndrome (AIDS). Another advancement in the management of HIV-seropositive (HIV+) patients is the ability to monitor the efficacy of CART with CD4+ helper T cells, ultrasensitive plasma HIV RNA levels, and antiretroviral resistance profiles which are now used commonly in clinic settings.

In addition, results from the Strategic Timing of Antiretroviral Therapy (START) trial (2) have proven the benefits and safety of early CART initiation on AIDS and non-AIDS related events in this international study of >4600 CART-naïve HIV+ individuals with CD4+ T cells counts > 500 cells/μL and HIV+ individuals with CD4+ T cells counts <350 cells/μL. CART is now begun as early as possible in an HIV+ patient, regardless of the CD4+ T cell counts.

The syndrome of HIV-associated neurocognitive disorders (HAND) was defined in 2007 with 3 stages of cognitive impairment: (1) asymptomatic neurocognitive impairment (ANI), (2) mild neurocognitive disorder (MND), and (3) HIV-associated dementia (3). ANI is defined by neuropsychological test performance that is at least 1 SD below the mean of demographically adjusted normative scores in at least two cognitive areas, but without impairment in everyday functioning. MND is defined by mild-to-moderate cognitive impairment with neuropsychological test performance that is at least 1 SD below the mean of demographically adjusted normative scores in at least two cognitive areas, and is associated with mild interference in daily functioning. HAD is defined by a moderate-severe cognitive impairment with neuropsychological test performance that is at least 2 SD below the mean of demographically adjusted normative scores in at least two cognitive areas, and is associated with marked interference with day-to-day functioning. The ANI category was added to this modified staging criteria by emphasize this mildest stage of cognitive impairment in CART-treated HIV+ patients (4).

CART is now the only option to prevent or delay progression of HAND, but it is effective in only a subset of patients. Indeed, in the START trial, early CART initiation did not have an effect on HAND (2). However, a recent study suggests that CART initiation very shortly after HIV acquisition results in greater improvement in HIV+ individuals' neurocognitive performance over time compared to deferred CART treatment 24 weeks later (5). HAND remains a common cause of cognitive impairment and persists in 15–55% of HIV+ individuals in the CART era (1). Over the past 20 years there has been little change in the overall prevalence of HAND (6). In the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort, HAND was present in 47% of the cohort, with ANI present in 33%, MND in 12%, and HIV-associated dementia in only 2% of the cohort. In the pre-CART era, HIV-associated dementia was the most common form of HAND. However, in CART-treated HIV+ patients the prevalence of HIV-associated dementia has declined substantially, and milder stages of HAND, *i.e.*, ANI and MND predominate (7).

Although HIV+ patients with the stage of ANI are asymptomatic, the stage may still be clinically relevant. In a CHARTER cohort study, HIV+ individuals who had a diagnosis of ANI at baseline were two to six times more likely to develop symptomatic HAND [(MND) and HIV-associated dementia] during several years of follow-up than those individuals who

were neurocognitively normal at baseline (8). However, confounding causes of cognitive impairment can contribute to the neuropsychological test impairment seen with ANI, so a diagnosis of ANI should be reserved for research studies, and not used in clinical settings.

In the past decade increasing attention is being given to HAND in resource limited settings. Almost 70% of the global HIV+ population resides in Sub-Saharan Africa, and multiple studies suggest that HIV+ individuals in this region have worse neurocognitive performance than HIV− individuals (1, 9–15). In a study among CART naïve HIV+ participants in Uganda 49% had HAND, with 20% of the cohort diagnosed with MND and 18% diagnosed with HIV-associated dementia (16). After two years on CART in this study from Uganda, 15% had HAND, with 10% of the cohort diagnosed with MND and only 2% with HIV-associated dementia. In another study of CART-naïve HIV+ individuals from South Africa, 42% of the cohort had MND and 25% had HIV-associated dementia. If these proportions are seen throughout resource-limited countries in the world, than HAND would likely be the most common form of neurocognitive impairment in young adults worldwide (1).

In the CART era, there have been significant changes in the clinical features of HAND. With respect to survival, the mean survival for an individual diagnosed with HIV-associated dementia in 1993–1995 was five months, but the mean survival for an individual diagnosed with HIV-associated dementia in 1996–2000 was 38.5 months (17). HIV+ patients diagnosed with HAND on current CART regimens have a near normal lifespan. However, it is not a full lifespan, as a population based study of 1602 HIV+ individuals demonstrated an approximately 3 fold increased mortality risk among individuals with HAND compared to individuals without HAND (18).

The temporal progression of HAND has also changed in the CART era. Prior to the use of CART, HIV-associated dementia was a rapidly progressive dementia. In HIV+ individuals on CART with a suppressed systemic viral load, the majority of individuals with HAND remain stable. In a four year study of 197 HIV+ participants receiving CART, 77% remained neurocognitively stable, 13% deteriorated, and 10% improved their neurocognitive performance (4).

Clinical features of HAND have also changed in the CART era. Extrapyramidal signs such as bradykinesia, rigidity, and tremor which were common in the pre-CART era in patients with HIV-associated dementia, are now less common in patients with HAND on CART.

The neuropsychological profile of HAND may also be different in CART-treated patients. The overall severity of cognitive impairment is milder, in HIV+ patients on CART. Also, the overall neuropsychological test profile may be different as well. In the pre-CART era, HAND was characterized as a subcortical disorder characterized by psychomotor slowing, motor dysfunction, and memory impairment. In the CART era, HAND may have a mixed pattern of both cortical and subcortical features with greater deficits in executive functioning and working memory (7).

Risk factors for HAND have also changed in the pre-CART era. Low CD4+ T cell count, high plasma and cerebrospinal fluid HIV RNA levels prior to antiretroviral therapy, HIV-related medical symptoms (*e.g.* anemia, low weight, and fatigue), and the presence of

extrapyramidal signs on neurological examination, depression, and psychomotor slowing on neuropsychological testing were all associated with an increased risk for dementia in HIV+ patients (19–21). In CART-treated individuals, many of these risk factors are no longer associated with HAND, as patients on CART have less immunosuppression and commonly have suppressed viral replication in both plasma and cerebrospinal fluid. Risk factors for HAND in the CART era include advanced age, a low CD4 nadir, cardiovascular risk factors, use of illicit drugs (*e.g.*, methamphetamine), sleep disorders as well as psychiatric comorbidly including depression and anxiety (1).

Despite the milder clinical phenotype, in the CART era, patients with HAND still have persistent abnormalities in the central nervous system even with systemic viral suppression. Biomarkers for HAND which remain elevated in CART-treated patients include cerebrospinal fluid (CSF) markers of inflammation such as neopterin (22), and markers of active axonal injury such as neurofilament protein light chain (23). Additional laboratory biomarkers of HAND currently under evaluation include markers of neuronal injury (*e.g.*, CSF quinolinic acid), immune activation (*e.g.*, plasma sCD14 and sCD163, CSF fractalkine, osteopontin and MCP-1), oxidative stress (*e.g.*, CSF ceramide, sphingomyelin, protein carbonyls), and energy metabolism (*e.g.*, CSF Krebs cycle substrates) (1, 24–29).

In addition, neuroimaging markers demonstrate both caudate/putamen atrophy and cortical atrophy in HIV+ individuals with suppressed viral load (30, 31). These structural changes in the brain indicate ongoing CNS injury in HIV+ patients despite systemic virological suppression of the HIV virus.

Autopsy studies of HAND in the CART era suggest that HIV encephalitis and neuronal loss do not explain the cognitive impairment seen in HIV+ patients on CART. In one study, the frequency of HIV encephalitis at autopsy was reduced from 54% in the pre-CART era to 15% in the CART era. The pathogenesis of HAND is associated with macrophage and microglial activation, increased cytokines, chemokines, glutamate, and neurotoxic viral proteins, and bioenergetics disturbance causing functional alterations in neurons rather than neuronal death (1). Additional discussion of the neuropathology of HAND can be found in the accompanying article by Dr. Benjamin Gelman.

An important demographic change in the CART era is the aging of the HIV+ population (32). As of 2015, more than one-half of all HIV-infected individuals in the United States are greater than 50 years old (33). In a study of 202 HIV+ adults in the Hawaii Aging with HIV-1 Cohort, older HIV+ individuals greater than age 50 years are twice as likely to have HIV-associated dementia compared to younger HIV+ individuals in an age range of 20 to 39 years (25). In the CHARTER study, age and HIV infection may have synergistic effects leading to worse performance on a summary measure of neuropsychological testing than either factor alone (33, 34).

Cerebrovascular disease risk factors such as hypertension, diabetes, and hypercholesterolemia are increasingly recognized as risk factors for cognitive impairment in HIV+ patients on CART. In the Multicenter AIDS Cohort Study (MACS) cohort, hyperglycemia and increased carotid intima media thickness as measured by carotid

ultrasound, a measure of large vessel atherosclerotic disease were both predictors of poor psychomotor speed performance among older HIV+ individuals (35). In another study, HIV + patients with pre-existing cardiovascular disease risk factors had a 6.2 fold higher odds of cognitive impairment compared to HIV+ patients without cardiovascular risk factors (36).

Neurodegenerative diseases such as Alzheimer's disease is another potential cause of cognitive impairment in patients with HIV infection. One autopsy study suggests that amyloid plaques are more frequently seen in HIV+ cases compared to age-matched HIV− control brains among subjects between age 30 and 59 years (37). Amyloid deposition also can be detected using position emission tomography (PET) radioligands, and studies of increased cortical uptake using the [^{18}F] AV-45 ligand in HIV+ individuals have been described (38). However, additional studies are needed to evaluate the association of amyloid deposition and cognitive impairment among older HIV+ individuals.

In summary, HAND remains a common neurological condition globally in the CART era. HIV dementia is rare in HIV+ patients with suppressed viral replication, and less severe forms of HAND predominate. The risk of HAND increases with age and when an HIV+ individual has cardiovascular risk factors. Latent HIV persists in the brain even when systemic virological control is achieved with CART, thereby hampering efforts to eradicate HIV, with the brain serving as a potential reservoir for the virus. Although many biomarkers have been evaluated, an easily obtainable, validated surrogate marker for HAND has not entered clinical practice in the CART era. The primary treatment for HAND remains CART, though trials for adjunctive therapies are ongoing.

Because of the changing phenotype of HAND, new animal models are needed to examine the pathogenesis and potential treatment for HAND. The remainder of this issue will describe some of these novel animal models for HAND.

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