EDITORIAL

The persistence of HIV-associated neurocognitive dysfunction and the effects of comorbidities

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Despite the effectiveness of combination antiretroviral therapy (CART), many HIV-infected patients continue to experience cognitive problems.[1] The study by Heaton et al.[2] in this issue of *Neurology*® examined HIV-associated neurocognitive disorder (HAND) in a large national cohort from the multicenter CHARTER study, which assesses the changes in presentation of HIV neurologic complications in the modern era of HIV treatment. Only 2% of the cohort exhibited dementia, confirming clinical observations that severe functional decline is now relatively rare.[1] Yet 47% of the sample without major comorbidities met criteria for HAND. It is notable that the latter prevalence is similar to those reported in studies conducted before modern antiretroviral therapy.[3] It is likely that this is partly attributable to the fact that HIV-infected patients are living longer with effective treatment, such that aging contributes to the prevalence of neurocognitive deficits. Nevertheless, the results provide clear evidence that HAND continues to be common despite the effectiveness of CART, and the prevalence of neurocognitive impairment is even greater when factoring in people with significant comorbidities commonly experienced by HIV-infected patients.

The study has a number of merits that make it likely to be considered a seminal investigation of HAND in the current era. The study employed a comprehensive set of validated neuropsychological tests with well-established norms. Diagnosis of HAND was conducted based on the up-to-date and widely accepted Frascati criteria.[4] The significance of the findings is also bolstered by the large sample size (n = 1,555) obtained from multiple centers, providing a representative cross-section of HIV-infected individuals in the United States. The use of a classification system for rating clinical comorbidities and their potential neurocognitive contributions[4] is another strength of the study. Accordingly, 15% of the sample was considered to have severe comorbidities that preclude a HAND diagnosis. The study employed 2 raters to establish the reliability of the comorbidity classification, which is a methodologic strength, and would be recommended for future studies that employ similar classification systems.

That a significant association between neurocognitive impairment and HIV disease variables was observed only for the individuals with minimal ("incidental") comorbidities is particularly interesting. Two possibilities may explain this finding. First, it is possible that the influence of HIV, though significant on its own, is relatively small in the context of the many comorbid conditions that can affect the brain, such as substance use, traumatic brain injury, and stroke. Additionally, a synergy between HIV infection and these comorbid conditions may exist which could amplify their impact on brain functioning, but which may not be apparent without explicit analysis of their statistical interactions. These 2 possibilities cannot be reconciled based on results from the current study, so additional studies are needed to address this question.

The importance of neurologic conditions such as stroke, traumatic brain injury, and seizure disorder in classifying the level of comorbid confounds is relatively obvious. While mounting evidence suggests that other conditions, including hepatitis C and substance abuse,[5] affect neurocognitive function, the mechanisms underlying these effects in conjunction with HIV are not well-understood. Furthermore, is not clear how the confounding impact of such factors can be judged, nor is it obvious that these comorbidities should be viewed as a basis for exclusion from a HAND diagnosis, given their importance to the clinical phenomena of HIV. Although the authors provide evidence of good interrater reliability of the comorbidity classification system, it should be noted that this is distinct from a demonstration of the validity of the classification, which is dependent on the scientific accuracy of the guideline for the classification system. It is therefore important that such guidelines be adjusted as our knowledge of these confounding conditions advances.

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The question remains as to why neurocognitive deficits remain prevalent in HIV-infected people despite immunologic and virologic controls afforded by CART. Inadequate penetration of CART into the CNS has been considered as a possible reason,[6] though findings from the current study did not support this hypothesis, so future longitudinal analysis of this cohort is needed to clarify this issue. Another possible explanation is the potential role of HIV disease history on current neurocognitive function, as evident here by the relationship between history of immune suppression (nadir CD4) and neurocognitive function. Additionally, nadir CD4 and duration of infection have been found to predict HIV-associated cerebral atrophy.[7]

Additional direct measures of the brain are necessary to further examine the etiology of HAND. Recent advances in MRI in conjunction with brain metabolite measures via magnetic resonance spectroscopy have considerable potential this regard,[7-9] and may ultimately provide biomarkers sensitive to neurocognitive and functional outcome. Furthermore, longitudinal studies are needed to track progression of neurocognitive function over time relative to other measures of brain health. Finally, given the apparent importance of comorbid conditions, the current study should also serve as a call for more intensive investigation of the assessment and treatment of hepatitis C, substance abuse, and other comorbidities in the context of HIV.

DISCLOSURE

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