HIV-Associated Neurocognitive Disorders: Still a Hot Topic?

Itzchak Levy MD

Unit of Infectious Diseases, Sheba Medical Center, Tel Hashomer, affiliated with Sackler Faculty of Medicine, Tel Aviv university, Tel Aviv, Israel

KEY WORDS: human immunodeficiency virus (HIV), asymptomatic neurocognitive impairment (ANI), dementia

IMAJ 2015; 17: 52–53

HAND (HIV-associated neurocognitive disorder) has frequently been discussed in the medical literature in recent years, but the way clinicians and researchers look at it changed over time. At the start of the AIDS epidemic when many people died with a clinical picture of severe AIDS-associated dementia, or as it was then called "AIDS dementia complex" (ADC), it was considered to be an AIDS-defining event complicating mainly severely immunosuppressed patients [1]. After the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s the incidence of ADC declined significantly, but many patients still suffered from a much lesser form of neurocognitive disturbance that eventually became known as HAND [2]. Now, as reviewed by Elbirt and colleagues in this issue of *IMAJ* [3], with modern antiretroviral therapy (ART) and probably due to earlier institution of ART in patients with a good CD4 count and many times during acute retroviral disease, even the frequency of HAND declined. Nevertheless, since HIV is a neurotrophic virus there is still much interest in its influence on the human brain.

According to many reviews in recent years the frequency of the more severe forms of HAND declined, but the less severe form, especially asymptomatic neurocognitive impairment (ANI), did not change [4]. According to the CHARTER study, 33% of people living with HIV may be diagnosed with ANI [5]. But what is the real clinical significance of this? I believe that "ANI" is overrated.

The problem is embedded in the characteristics of the tests that are used to assess neurocognitive function (NCP) and in the way that ANI is defined – i.e., people with no clinical disturbance. HAND in its more severe forms impairs many domains in cognitive function, including memory, learning, attention, and executive and motor functions. ANI is defined as an asymptomatic condition defined solely by an abnormality (which means at least 1 standard deviation below the mean of scores in a healthy population). However, there are several problems with this definition.

The first problem lies in the characteristics of the tests: neuropsychology tests to detect cognitive dysfunction (e.g., Trail A and B, grooved pegboard test, stroop test, memory tests, etc.) are not pure indicators of cognition, and unfortunately their results may be influenced by many factors including age, gender, education, culture, socioeconomic status, psychoactive drugs, malingering, medical illness, drugs including ARTs, psychiatric status, premorbid functional level, and more. Many of these factors are common in people living with HIV, so to say that a certain test abnormality results from the direct effect of the HIV on the central nervous system (CNS) is almost impossible. The second problem is the lack of a good control group in most studies. The best control group would be a similar group of people, with matched age, cultural and educational background, sexual orientation, etc., who were tested in the same setting; however, such control groups were never matched. Another problem is that the definition of ANI is not stringent, and this results in approximately 20% of the population being classified as abnormal, an unacceptable false-positive rate [6].

Nevertheless, the entry of HIV into the CNS and its persistence there are extremely important in patients with CNS symptomatic disease, even in those with undetectable viral load in plasma and a good CD4 cell count. In recent years there have been numerous reports on subjects with HIV escape in the cerebrospinal fluid (CSF) even though they did not have AIDS or demonstrate severe immunosuppression on routine blood tests. Many of those patients are diagnosed with encephalitis or severe neurocognitive impairment [7]. This proves that HIV can progress differently in different compartments, and this should be taken into consideration when prescribing HAART. But, as Elbirt and co-authors contend in their present review, HAART is apparently not sufficient to prevent or reverse HAND, and therapy with a combination of drugs with high CNS penetration effectiveness score (CPE) should be considered while adjunctive and alternative therapies are being explored. It will be interesting to see if HAND will be impacted by the introduction of integrase inhibitors, which are overwhelmingly replacing nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Clearly, further research is needed – but with more emphasis on clinical outcomes.

Correspondence
Dr. I. Levy
Unit of Infectious Diseases, Sheba Medical Center, Tel Hashomer 5262100, Israel
email: itsik.levi@sheba.health.gov.il

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