EDITORIAL

NeuroAIDS in West Africa: A Full Circle

Can. J. Neurol. Sci. 2007; 34: 118-119

Over 38 million people are currently infected by the human immunodeficiency virus type 1 (HIV-1) (www.unaids.org). Human immunodeficiency virus type 1 is a retrolentivirus causing immunosuppression, which progresses to the acquired immunodeficiency syndrome (AIDS) and eventual death. HIV-1's origins in human lie in its evolution from the simian immunodeficiency virus infection in nonhuman primates and subsequent transmission to humans in central Africa, likely through the bushmeat industry. HIV infection has ravaged sub-Saharan Africa exerting profound health, social, economic and political effects that will last for generations. HIV-1 is *neurotropic* (infects the nervous system) and is *neurovirulent* (causes disease in the nervous system).[1] The nervous system is infected immediately after primary HIV infection with rapidly ensuing subclinical neurological injury. In fact, the severity and frequency of HIV-induced neurological disorders are influenced by host *neurosusceptibility*, which are determined by factors including host age, genetic polymorphisms, level of immunosuppression and concurrent infections, together with the ability of the host to contain infection at the time of primary infection.[2] HIV-1's primary central nervous system manifestations, directly caused by the virus, include HIV-associated dementia (HAD), which affects 20% of untreated and 5-10% of antiretroviral-treated HIV/AIDS patients and the less severe and antecedent condition, HIV-induced Minor Cognitive-Motor Deficit, which affects another 25-30% of HIV-infected patients, regardless of combination antiretroviral therapy (ART) implementation. These disorders are defined by cognitive, behavioral and motor deficits, similar to other 'subcortical' syndromes and are associated with diminished quality of life and increased health care costs. The remaining approximately 50% of patients exhibit no deficits of cognitive or brain function but HIV-induced peripheral nervous system disorders, particularly a distal sensory polyneuropathy, have become major clinical issues in recent years, affecting over 35% of infected patients.

These neurological disorders occur in HIV-infected patients globally with similar frequencies in different geographic sites, seemingly irrespective of the HIV-1 clade (subtype). With the increasing availability of ART, the incidence and severity of HAD has declined while the prevalence of both HAD and HIV-associated sensory neuropathy is increased because persons with HIV/AIDS are living longer.[3-6] Nonetheless, the development of HIV-induced CNS disease heralds a worsened survival prognosis with or without concurrent ART.[7-8] In the era of combination ART, the onset of HAD is occurring at earlier stages of the HIV/AIDS disease course with progressively higher levels of immune competence ($CD4^+$ T cell levels 200-400 cells/μl) at the time of diagnosis. Neuronal death and injury including synaptodendritic 'pruning' are the prototypic consequences of chronic inflammation induced by HIV-1 within the brain and are among the neuropathological hallmarks of HAD (reviewed in[9]). Complementing the persistence of clinical neurological disease despite ART's beneficial effects on viral replication and immunity, a surprising degree of ongoing neuroinflammation persists in patients receiving ART.[10] This may reflect poor CNS penetration by ARTs but perhaps also emergence of neurovirulent HIV strains in the brain.

Although the neuropsychological sequelae of HIV infection are well characterized[11] and tend to reflect disruption of frontal cortico-basal ganglion-thalamic functions, little is known about the impact of HIV infection on neuropsychological performance among peoples outside of industrialized countries. Studies from East Africa indicate similar frequencies and severity,[12,13] of neuropsychological and neurological deficits caused by HIV infection. Nothing is known about HIV's effects on neuropsychological performance on West African populations despite substantial evidence indicating that the global HIV epidemic has its origins in the central and western Africa.[14] Hence the study by Odiase et al[15] from the University of Benin in Nigeria in the present issue of the Canadian Journal Neurological Sciences is highly relevant, given that Nigeria is exploding in terms of population and economic growth with increasing rates of HIV infection. Indeed, Nigeria represents an interesting site for studies of HIV infection because both HIV-1 and -2 are present in its population as well as multiple subtypes (clades) of HIV-1.[16] Odiase and colleagues[15] report a cross-sectional study of neuropsychological performance in a range of HIV-infected asymptomatic and symptomatic subjects together with age-, education level- and sex-matched healthy HIV seronegative controls, drawn from a teaching hospital. Using a computer-assisted neuropsychological battery of tests the authors show that HIV-infected subjects exhibited impaired attention and delayed response times, regardless of whether or not, they were symptomatic from their HIV infection. Memory function was intact among asymptomatic HIV seropositive subjects but was worsened if patients were symptomatic. Moreover, neuropsychological performance declined with lower blood $CD4^+$ T cell levels, underscoring the close relationship between reduced immunity and declining neuropsychological performance in HIV/AIDS patients. Despite these interesting findings, there are several shortcomings within the present study, also evident in other recent neuroAIDS studies from Africa.[17] These include the absence of correlative neuroimaging to exclude space–occupying lesions, the lack of information about HIV type and clade and lastly, any prospective outcomes among individual study groups. Indeed, the likelihood of an opportunistic CNS infection confounding these studies is substantial.[18] Nonetheless, the findings from this Nigerian group recapitulate many reports from industrialized countries in terms of worsened neuropsychological performance caused by HIV infection in association with reduced immune status. Moreover, this study also extends the recognition of the magnitude of HIV-mediated neurological disease throughout the world. It will be important in the future to assess the impact of ART in this group

of patients as different ART regimens become more available globally. Other useful studies to be performed in the same setting might include analyses of the broader frequency and impact of HIV-mediated diminished neuropsychological performance on economic and social status, permitting governments to plan appropriate interventions as required. This is reasonable in Nigeria, assuming its continued economic growth. However, the burgeoning frequency of HIV infection and its adverse effects in countries like Nigeria, which have been until recently comparatively spared the devastation of HIV infection over the past two and a half decade duration of the global epidemic, underlines the importance of continued efforts to prevent new HIV infections. Given Canada's relative success in limiting the spread of HIV infection with only 56,000 infected individuals at present and its large economic resources, it is timely and more importantly, morally imperative that the Canadian government has recently partnered with the Bill & Melinda Gates Foundation to create an HIV vaccine initiative (Globe and Mail, February 21, 2007). It is anticipated that this joint venture will contribute to the control and eventual eradication of the HIV/AIDS epidemic through the development of new vaccines and related prevention strategies.

Christopher Power
Edmonton, Alberta

References

1. Power C. Retroviral diseases of the nervous system: pathogenic host response or viral gene-mediated neurovirulence? Trends Neurosc. 2001;24(3):162-9.
2. McArthur JC, Brew BJ, Nath A. Neurological complications of HIV infection. Lancet Neurol. 2005;4(9):543-55.
3. Dore GJ, Correll PK, Li Y, Kaldor JM, Cooper DA, Brew BJ. Changes to AIDS dementia complex in the era of highly active antiretroviral therapy. Aids. 1999;13(10):1249-53.
4. Ferrando S, van Gorp W, McElhiney M, Goggin K, Sewell M, Rabkin J. Highly active antiretroviral treatment in HIV infection:benefits for neuropsychological function. AIDS. 1998; 12:F65-70.
5. Tozzi V, Balestra P, Galgani S, Narciso P, Ferri F, Sebastiani G, et al. Positive and sustained effects of highly active antiretroviral therapy on HIV-1-associated neurocognitive impairment. Aids. 1999;13(14):1889-97.
6. Sacktor N, Lyles RH, Skolasky R, Kleeberger C, Selnes OA, Miller EN, et al. HIV-associated neurologic disease incidence changes: Multicenter AIDS Cohort Study, 1990-1998. Neurology. 2001;56(2):257-60.
7. Price RW, Yiannoutos T, Clifford DB, Zaborski L, Tselis A, Sidtis JJ, et al. Neurological outcomes in late HIV infection:adverse impact of neurological survival and protection effect of antiretroviral therapy. AIDS. 1999;13:1677-85.
8. Letendre SL, McCutchan JA, Childers ME, Woods SP, Lazzaretto D, Heaton RK, et al. Enhancing antiretroviral therapy for human immunodeficiency virus cognitive disorders. Ann Neurol. 2004;56(3):416-23.
9. Jones G, Power C. Regulation of neural cell survival by HIV-1 infection. Neurobiol Dis. 2006;21(1):1-17.
10. Anthony IC, Ramage SN, Carnie FW, Simmonds P, Bell JE. Influence of HAART on HIV-related CNS disease and neuroinflammation. J Neuropathol Exp Neurol. 2005;64(6): 529-36.
11. Selnes OA. Memory loss in persons with HIV/AIDS: assessment and strategies for coping. AIDS. Read 2005;15(6):289-92, 294.
12. Maj M, Satz P, Janssen R, Zaudig M, Starace F, D'Elia L, et al. WHO Neuropsychiatric AIDS study, cross-sectional phase II. Neuropsychological and neurological findings. Arch Gen Psychiatry. 1994;51(1):51-61.
13. Sacktor N, Nakasujja N, Skolasky R, Robertson K, Wong M, Musisi S, et al. Antiretroviral therapy improves cognitive impairment in HIV+ individuals in sub-Saharan Africa. Neurology. 2006; 67(2):311-14.
14. Sharp PM, Bailes E, Chaudhuri RR, Rodenburg CM, Santiago MO, Hahn BH. The origins of acquired immune deficiency syndrome viruses: where and when? Philos Trans R Soc Lond B Biol Sci. 2001;356(1410):867-76.
15. Odaise FE, Ogunrun OA, Ogunniyi, AA. Memory performance in HIV/AIDS - a prospective case control study. Can J Neurol Sci. 2007;34(2):154-159.
16. Zeh C, Pieniazek D, Agwale SM, Robbins KE, Odama L, Sani-Gwarzo N, et al. Nigerian HIV type 2 subtype A and B from heterotypic HIV type 1 and HIV type 2 or monotypic HIV type 2 infections. AIDS Res Hum Retroviruses. 2005;21(1):17-27.
17. Wong MH, Robertson K, Nakasujja N, Skolasky R, Musisi S, Katabira E, et al. Frequency of and risk factors for HIV dementia in an HIV clinic in sub-Saharan Africa. Neurology. 2007; 68(5):350-5.
18. Bhigjee AI. Neurological manifestations of HIV infection in Kwazulu-Natal South Africa. J Neurovirol. 2005;11 Suppl 1: 17-21.