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EDITORIAL

HIV and aging

Avindra Nath

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The introduction of antiretroviral therapy has dramatically changed the clinical and epidemiological features of HIV infection. It has transformed the illness from a subacute fatal illness to a chronic survivable illness whereby patients can live with the infection for several decades. Thus, patients are living into the later decades of life and the effects of infection are complicated by the effects of aging. For example, the proportion of affected patients greater than 65 years of age grew 10-fold in the years between 1994 and 2004 in the US. Bhatia et al. reviewed the challenges of older populations in the era of antiretroviral therapy. They cite that by the end of 2008, nearly 50 % of HIV-infected patients were over 45 years of age and this population will continue to grow. The process of aging also leads to an increased proinflammatory environment in the brain and other organ systems. Further, aging may itself be accelerated by HIV infection and thus complications associated with the aging process may be seen in younger age groups within this population. As a result, they develop frailty, a syndrome of weakness, exhaustion, unintentional weight loss, decreased strength, and/or slowness which may be accelerated by about 10 years. At the molecular level, there is evidence of telomere shortening in HIV-infected patients, immunosenescence, and increased deposition of amyloid plaques in the brain in younger age groups. Realizing the importance of this comorbidity on society, the scientific community has taken several initial steps to stimulate research in this field. The National Institutes of Health has provided targeted funding for this field of research. A conference was recently held exclusively on this topic (www.virology-education.com) and the *Journal of Neurovirology* has put together this special issue devoted to this subject.

The review by Wendelken and Valcour focuses on the effects of aging on neuropsychological function in HIV-infected patients. While it appears that there may be increased neuropsychological impairment in these patients, the causes might be multifactorial. This may include Alzheimer's like pathology, cerebrovascular disease, exposure to antiretroviral drugs, and prior use of drugs of abuse and other comorbidities. The neuropsychological dysfunction typically has psychomotor slowing, problems with attention and concentration, executive dysfunction, and impairment of learning and recall, with sparing of semantic and visuospatial abilities. New infections can also occur in the elderly, but are often missed, leading to longer unsuppressed HIV infection and thus more risk for cognitive impairment. The authors point out that interpretation of some of the published

A. Nath (✉)
Section of Infections of the Nervous System,
National Institute of Neurological Disorders and Stroke, NIH,
Bethesda, MD, USA
e-mail: natha@mail.nih.gov

studies is difficult since they have did not include enough patients greater than 60 years of age.

Epidemiological evidence suggests that there is an increasing incidence of ischemic stroke in HIV-infected patients. Cruse at al. reviewed the epidemiological, clinical, and autopsy data from the pre- and post-HAART era to show that there may be an important association between HIV infection and HAART therapy with stroke. Data suggests that not only is the incidence of stroke increasing, but rather, ischemic stroke seems to be occurring in a younger age group compared to non-HIV-infected patients.

Neuropsychiatric complications in the aging HIV population have not been well studied, as reviewed by Watkins and Treisman. However, these complications have the potential to result in a major impact on morbidity and mortality of these patients. Some studies suggest that the incidence of depression may be greater in this population. This poses the risk of non-compliance with medications, and the paucity of other health interventions. The authors point out that depression has been linked to increased substance abuse and increased cardiovascular complications. Depression may also have adverse effects on the immune system thereby enhancing the complications of HIV infection. Further, some of the antiretroviral drugs and other medications often used in this patient population may cause neuropsychiatric symptoms and these patients seem to be more vulnerable to such side effects. Hence, there is great need for research in this area.

Holt et al. reviewed the neuroimaging abnormalities in patients with HIV infection and the effect of aging. It shows that the frontal and temporal lobes are the most vulnerable to these effects. Age-related changes are evident despite the use of antiretroviral therapy. Most interpretations are based on cross-sectional studies as there is a paucity of longitudinal studies to determine the effects of age on HIV infection of the brain. Several neuroimaging parameters including structural and metabolite changes show good correlation with age-related changes and neurocognitive dysfunction. Further, these techniques are also able to demonstrate abnormalities in the brain even when neurocognitive testing fails to detect any dysfunction suggesting that the neuroimaging techniques could serve as an important surrogate marker.

In a cross-sectional study, Nakamoto et al. used diffusion tensor imaging to examine the microstructural differences associated with cerebrovascular risk factors in HIV-infected patients aged 50 years and older. Their findings suggest that subtle microstructural brain abnormalities are present in the caudate and hippocampus in subjects with comorbid impaired glucose tolerance. Importantly, several other cerebrovascular risk factors were also studied but they failed to show such correlation with the brain abnormalities. However, it is possible that the relative importance of these other factors may become apparent in larger sample sizes or longitudinal studies.

To determine if aging-related cognitive decline was related to maladaptive stress responses due to abnormal regulation of glucocorticoid receptor expression in the brain, Soontornniyomkij et al. studied the expression of molecular chaperons, namely FKBP51 and 52, which control glucocorticoid receptor sensitivity by immunohistochemistry in autopsy brain tissue. They found that FKBP51, but not 52, was expressed in increased amounts in HIV-infected patients with or without neurocognitive impairment when compared to controls. However, there was no correlation with age suggesting that while this pathway may be important for maladaptive stress responses in HIV-infected patients, other factors may be responsible for age-related changes.

Genetic factors may also influence the development of cognitive impairment. In older HIV-infected patients, the ApoE4 allele has been associated with neurocognitive dysfunction. Martinez et al. used an experimental system to show that HIV may directly impair neurogenesis particularly in neuroprogenitor cells derived from individuals with the ApoE3/4 allele. In this study, they did not find a similar effect on neuroprogenitor cells with the ApoE4/4 allele, but this may be due to the small sample size of specimens with this genotype.

Another area that deserves attention is the effect of aging on neuromuscular complications associated with HIV infection. Robinson-Papp et al. reviewed the literature to show that both aging and HIV infection in themselves can cause peripheral nerve dysfunction and muscle disorders and longitudinal studies suggest that old age may be a risk factor independent of other covariates for its association with peripheral nerve dysfunction. Antiretroviral drugs may further contribute to these symptoms. Comorbidities such as diabetes and renal dysfunction are associated with aging and may also contribute to the neuromuscular dysfunction. In patients with HIV infection, mitochondrial dysfunction and proinflammatory changes can be found both at the level of the dorsal root ganglia as well as the distal axon. However, clinical and pathophysiological studies are necessary to determine the combined effects of HIV infection and aging.

Despite advances made in our understanding of the effects of aging on HIV neuropathogenesis, several important questions remain unanswered. The critical pathophysiological mechanisms that lead to acceleration of the aging process in HIV-infected patients need to be determined. Clinical studies with older individuals are also necessary to better understand the effects of HIV infection in this population and develop strategies for pharmacological and social intervention.