J. Neurovirol. (2011) 17:1–2
DOI 10.1007/s13365-010-0015-0

EDITORIAL

Changing pattern and pathophysiology of cognitive dysfunction with HIV infection in the era of antiretroviral therapy

Avindra Nath

Received: 13 December 2010 / Accepted: 13 December 2010 / Published online: 19 January 2011

With the introduction of combination antiretroviral therapy (CART), there was a dramatic decline in all forms of neurological complications of HIV infection. In fact, immune suppressed individuals with neurocognitive impairment showed improvement in cognition following treatment with antiretrovirals. However, it is becoming increasingly evident that despite excellent virological control, milder forms of neurocognitive impairment seem to be on the rise. To address this concern, at the request of the editor-in-chief, Kamel Khalili, I undertook the task of putting together a special issue of the *Journal of Neurovirology* that would address the current epidemiology, clinical manifestations, pathophysiology, and treatment of HIV-associated neurocognitive disorders (HAND). I am grateful to the authors who were invited to submit their research for this issue and to the reviewers, editorial staff, and publishers for getting this issue together in record time. I am particularly grateful to Dr. Khalili for his guidance throughout the process.

In this issue, Heaton and colleagues compared the epidemiology and clinical pattern of neurocognitive impairment in a cohort of nearly 900 patients, each from the pre- and post- (CART) era. They found that in the asymptomatic stages of HIV infection (CDC stage A), the rate of neurocognitive impairment increased from 25% to 36% in the post-CART era. There was less motor impairment and more impairment of memory and executive function. There was no longer a correlation with viral load but nadir CD4 cell counts continue to be a risk factor. This suggests that viral entry into the brain during periods of immune suppression may be key to driving this impairment possibly due to immune reconstitution or by viral products that are not impacted by CART. Another symptom that seems to have been under appreciated previously in these populations is fatigue. Schifitto et al. found that 64% of individuals with HAND also have significant fatigue. The presence of fatigue did not correlate with viral load but correlated with lower levels of creatinine in the basal ganglia as determined by magnetic resonance spectroscopy (MRS) which suggests impaired energy metabolism. In an autopsy study, Kumar et al., found that dopamine levels were significantly decreased in the substantia nigra and correlated with HAND and increased viral loads in the basal ganglia. Zou et al., studied the mechanism by which HIV-gp120 causes neurotoxicity of striatal neurons. They observed that striatal neurons express both chemokine receptors CXCR4 and CCR5 that interact with gp120 and cause neurotoxicity via phosphorylation of Akt. They suggest that Akt may be a therapeutic target. Consistent

A. Nath
Department of Neurology and Neuroscience,
Johns Hopkins University,
Baltimore, MD, USA

A. Nath (✉)
Division of Neuroimmunology and Neurological Infections,
Johns Hopkins University,
Baltimore, MD, USA
e-mail: anath1@jhmi.edu

with the above observations, Moore et al. report that chronic HIV infection rather than acute infection results in HAND. Considering the importance of these chemokine receptors in HIV neuropathogenesis, Avdoshina et al. examined the regional expression of these receptors in the brain and discovered that neurotrophins such as NT3, NGF, and BDNF modulate their regional distribution. Since neurotrophin levels maybe diminished in HIV-infected individuals, this may represent a novel mechanism for causing cerebral dysfunction.

Letendre et al. found that a cohort of patients that were virologically controlled (CSF HIV viral load <50 copies per milliliter) had elevated levels of IP-10 (CXCL10) and IL-8 (CXCL8) which correlated with markers of neuronal dysfunction and glial cell activation as determined by MRS. Fractalkine (CX3CL1) levels correlated with severity of dementia. Since CXCL10 is a chemokine for lymphocytes and CX3CL1 is a chemokine for leukocytes and CXCL8 is produced by activated lymphocytes, these findings support the possibility that immune reconstitution with lymphocyte infiltration may result in neuroglial cell dysfunction. Cowley et al., studied the diversity of the HIV-Tat sequences in the brain and other tissues from five patients with HIV dementia. There was no significant difference between the HIV-LTR transactivation properties of the CNS and non-CNS Tat. The effect on neurotoxicity was not studied. Several mutations were found in the 31–61 region of Tat which contains the neurotoxic domain. Within this domain, the Cys-rich region was conserved in all brain derived sequences but single mutations in the Arg-rich regions were found in 3/13 brain-derived sequences but not in the non-brain clones. The significance of this is unclear. In an accompanying paper by Gray et al., a similar approach was taken to study the HIV-nef gene from seven patients with HIV dementia. In contrast to Tat, nef showed compartmentalization within the CNS and reduced genetic heterogeneity compared to non-CNS-derived sequences. The functional significance of this compartmentalization is unclear, since the ability of the nef genes to downregulate CD4 and MHC-I antigen was conserved in all tissues. Only one patient had a truncated nef protein in the brain. Further, astrocyte infection is CD4 independent, hence the functional significance of the brain-specific nef sequences need to be further studied in this cell type. In an effort to identify HIV genetic changes that may predict the development of HAND, Li et al., extensively studied a single individual prospectively and found that in peripheral blood-derived HIV LTRs, the presence of a C to T change at position 3 of C/EBP site I and at position 5 of Sp site III predicted the onset of HAND. This was also associated with a shift in CXCR4 to CCR5-tropic virus.

Malaspina et al. identified a unique cohort of HIV-infected individuals >45 years of age, one third of whom did not have any neurocognitive impairment. Further studies of similar cohorts may help identify factors that can protect against HAND. In an SIV model, Graham et al. show that early treatment with CART prevents the development of CNS disease.

Collectively these studies suggest that in the absence of comorbidities, the increased rates of HAND despite CART may be attributed to chronic HIV infection of the brain resulting in a chronic immune reconstitution within the brain. Although the role of immune reconstitution needs to be further studied in longitudinal cohorts, significant advances have been made in understanding the molecular basis of HIV-induced neuronal injury with identification of novel therapeutic targets. However, importantly, these studies also support early intervention with CART for prevention of subsequent development of HAND.