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Guest Editorial

HIV and HIV Dementia

Long before the discovery of the human immunodeficiency viruses, HIV-1 and HIV-2, studies with visna virus and other lentiviruses of ruminants established that neuroinvasiveness and neurovirulence are a characteristic of lentiviral infections (Nathanson, 1998). Soon after the first descriptions of the acquired immunodeficiency syndrome (AIDS), landmark studies by Price and others (Price *et al*, 1988) established the importance of neurological symptomatology in a significant proportion of HIV infected individuals. The neurological deterioration attributed to HIV infection itself (as opposed to the problems associated with opportunistic infection) has been described extensively in many reviews, but can be briefly summarized as a subcortical dementia, differing from cortical dementias by the tendency for memory impairment to occur after other cognitive symptoms like inattention, indifference, and psychomotor slowing (reviewed in Atwood *et al*, 1993; McArthur *et al*, 1994), and by prominent motor abnormalities like incoordination. This symptom complex has been termed the AIDS Dementia Complex (ADC), or HIV Dementia (HIVD). Its neuropathological correlate, HIV encephalitis (HIVE), consists of a constellation of findings that includes myelin pallor, astrocytosis, and most specifically for HIV infection, the formation of multinucleated giant cells (MGC's) that are thought to be the result of syncytia formation between infected macrophages and microglia (Sharer, 1992; Wiley and Achim, 1994). Syncytia formation is a common tissue culture signature for HIV infection and is the result of the interaction between the viral envelope proteins (gp120 and gp41) and the cellular receptors for the virus.

HIVD can be distinguished from virtually all other viral diseases of the nervous system by its chronicity, by the relative paucity of infected cells, and by the limited if any evidence of neuronal infection in spite of widespread motor and cognitive deterioration. Virus is instead concentrated in microglia and macrophages, with some contribution from infection of astrocytes and endothelial cells (Gabuzda *et al*, 1986; Wiley *et al*, 1986). This unusual cellular distribution of infection is the most problematic finding in attempting to understand the pathophysiology of this condition. Furthermore, attempts to correlate the frequency of HIV infected microglia with disease have been inconclusive (Glass *et al*, 1993, 1995; Wiley and Achim, 1994; Brew *et al*, 1995; Johnson *et al*, 1996), leading to the proposal that unknown factors or neurotoxins, probably arising from microglia, are responsible for neurological deterioration (Giulian *et al*, 1993). Many investigators also believe that microglial activation is as important as microglial infection in the pathogenesis of HIVD.

Potential neurotoxins that could arise from microglia include viral proteins like gp120, gp41, and tat, and a host of secretory products like platelet activating factor, tumor necrosis factor alpha, and many others (Giulian *et al*, 1993, 1996; Gelbard *et al*, 1994; Genis *et al*, 1992; Adamson *et al*, 1996). Proposed mechanisms for neurodegeneration include apoptosis, induction of nitric oxide synthase and activation of NMDA receptors. However, in spite of over a decade of research into this area, there is no consensus on any one toxin, or even if a combination of secretory products is ultimately responsible for the problem.

Unraveling the mechanism of HIVD is a fascinating and ultimately worthwhile scientific pursuit, as this infection may be prototypic of neurodegeneration mediated by inflammatory cytokines and chemokines, and its elucidation may help understand other diseases where microglial activation plays an important role. Among these are Multiple Sclerosis, neurotrauma, and Alzheimer's disease.

However, from the more immediate point of view of treatment and management of individuals with HIV infection, there are more pressing questions that directly address the critical role of the virus itself in mediating this complication. Anecdotal reports have suggested that HIV penetrates the CNS early in the course of infection (Davis *et al*, 1992), and genetic analysis from several groups indicates that virus within the CNS evolves somewhat independently of peripheral virus (Epstein *et al*, 1991; Hughes *et al*, 1997), indicating a certain degree of sequestration, perhaps for long periods of time. With the increasing understanding of the central importance of viral replication in the development of immunodeficiency (Ho *et al*, 1995), the rest of the HIV research community has focused on viral load, viral phenotype, and viral latency as critical areas that need better elucidation. In terms of research into the pathogenesis of HIVD, it is time to pay closer attention to these issues. More specifically, (1) Does viral load in either the CSF or the brain parenchyma, or both correlate with the development of HIVD? (2) Are there any specific viral phenotypes or genotypes that are particularly neuroinvasive or neurovirulent? (3) Which anti-retrovirals are likely to contribute most to clearance of virus in the CNS? and as

a corollary (4) Is the CNS a 'sanctuary site' for HIV? As with much of HIV research, the exciting findings regarding the role of chemokine and other G-proteins coupled receptors in viral entry are likely to direct the thinking in at least some of these areas. It is also entirely possible that the pathophysiology of HIVD may never be completely elucidated, except perhaps for a clarification of the role of virus in its etiology, before it is cured thanks to the advent of highly active antiretroviral therapy (HAART).

This special issue of the *Journal of Neurovirology*, which includes both individual articles and abstracts for the Conference on the Neuroscience of HIV infection, indicates that investigators have understood the importance of these questions, and are beginning to address them in humans, and in the best animal model available, simian immunodeficiency virus infection of non human primates.

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