



Viral and immunological factors involved in HIV neuropathogenesis

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Many HIV-infected individuals develop symptoms of neurologic disease after long-term infection. The viruses isolated from the cerebrospinal fluid of these individuals show biologic and serologic differences from viruses recovered from the blood. The brain-derived viruses are macrophage-tropic, generally not cytopathic for T lymphocytes, and do not decrease CD4 molecule expression. The pathogenesis in the brain suggests the virus passes through the blood-brain barrier (via endothelial cells) to establish infection in microglial cells/macrophages and perhaps to infect and disturb the function of astrocytes and oligodendrocytes. The infection can induce the release of cytokines by the HIV-infected cells as well as immune cells responding to the HIV infection. These cellular products can be toxic to the brain. In addition, viral proteins such as envelope, Tat, and Nef can have toxic

effects in the CNS. They can interrupt normal intercellular communications or induce cell death via direct cytotoxicity or apoptosis. In some cases, humoral immune responses, such as autoantibodies induced by HIV, could cause CNS disease. Moreover, cytotoxic CD8+ cells may be responsible for direct damage to the brain. Finally, other infections in the brain (e.g., CMV, HPV) could play a role in disease induction in the CNS. The effects of antiviral therapy, such as AZT, on reducing AIDS dementia and other neurologic findings suggest an effect of these drugs either on virus replication or on cytokine production in the central nervous system. Approaches at defining the events causing neurologic AIDS are critical in developing appropriate therapies for HIV infection and its pathogenesis in the CNS.