Journal of NeuroVirology, 8(suppl. 1): 2–3, 2002
 ISSN 1355–0284/02 $12.00+.00
DOI: 10.1080/13550280290049769

Plenary Session 1

Molecular biology of HIV-induced CNS disease/HIV disease and clinical investigation

Chairpersons: K. Khalili (Philadelphia, USA)
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Cellular and viral factors involved in HIV-1 CNS disease progression

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Although HIV-1 infection of CD4+ T lymphocytes in the peripheral blood and lymphoid tissue plays a central role in AIDS, other cellular compartments participate in the pathogenic process, including the cells of the monocyte/macrophage lineage. Viral infection of this cellular lineage likely facilitates evasion of the immune response, maintains a reservoir of proviral DNA during continuous therapy, and provides one vehicle for delivery of virus to the CNS within activated components of this lineage. Subsequent to viral entry into the CNS, perivascular macrophages and resident brain microglial cells, and astrocytes represent the primary sites of infection with the overall level of viral gene expression dictated by the nature of the viral swarm, cellular phenotype, extracellular signaling molecules and other patient-specific physiologic processes. Viral gene expression within the monocytic lineage is critically dependent on the regulation of the HIV-1 LTR, which represents the promoter element that drives expression from proviral DNA to guide the synthesis of potential toxic viral proteins and infection virus. Clearly, factors that guide the level of LTR-directed transcription would include genomic sequence variation within the regulatory unit, alteration of the level and specific activity of cellular transcription factors during the course of cellular differentiation and activation, the complex network of CNS extra- and intracellular signaling pathways that converge on the LTR, and the relative specific activities of the trans-activator Tat and the virion-associated protein Vpr. Modulators that converge on the LTR and affect expression and replication have downstream effects including cytokine dysregulation, production of neurotoxic proteins (Tat, gp120 and Nef), and disruption of cellular function, which ultimately leads to the deregulation of other cell populations (such as astrocytes, neurons, brain endothelial cells) and progressive deterioration of brain function. We propose that co-evolution of the viral LTR and the viral proteins Tat and Vpr within cells of the myeloid lineage play an important role in the genesis of HIV-1-associated dementia (HIVD).

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Molecular analysis of viral RNA in MNGCs

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Molecular analysis of virus strains obtained from the CNS, particularly those that replicate in microglia or brain macrophages can provide important information regarding the potential requirements for neurovirulence. Workers from several laboratories have shown that isolates and viral genomes from the CNS evolve separately from peripheral tissue, and that some phenotypic properties, such as capacity to induce neurotoxicity, vary among different isolates.

SIV-infected macaques develop an encephalitis (SIVE) that is pathologically virtually indistinguishable from that associated with HIV infection, with multinucleated giant cells (MNGC) being the principal histopathological manifestation. To dissect SIV variants responsible for the development of MNGCs, we examined the relationships between env sequences transcribed in individual MNGCs and those from genomic DNA of brain and spleen tissues. The brain-specific variant found in all brain clones was dominant among the clones from MNGCs, suggesting a role in the formation of giant cells. Furthermore, two additional minor groups of sequences were present in MNGCs. One group consisted of sequences closely related to those from spleen implying recent and probably multiple episodes of neuroinvasion. The second group represented clones similar or identical to the initial inoculum. Survival of archival sequences and their activation presumably by the fusion of productively and quiescently infected macrophages/microglia identify the CNS as a possible anatomical reservoir for latent infection.

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HIV-1-associated encephalopathy: a subcortical dementia

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HIV-1-associated encephalopathy is characterized by motor, cognitive and emotional deficits. Motor deficits appear very early during the course of the disease, have been proven to

predict AIDS-manifestation, clinically overt dementia and death and therefore are the predominant symptoms of HIV-1-associated dementia, which has been supposed to be mainly subcortical. This hypothesis has been supported by the results of electrophysiological, neuropsychological, neuroradiological, cerebrospinal fluid and biochemical examinations. These methods point out a basal ganglia dysfunction in HIV-1-positive patients. In basal ganglia dysfunction, there is a patholgical change in con- and divergence of informations. Under physiological conditions, there is an intense interaction between basal ganglia and the cortex; informations are processed in parallel loops. In basal ganglia dysfunction neuronal excitation spreads from one loop into others in the immediate neighbourhood. The receiving loop takes over information from too many senders and vice versa. Excitation is distributed unprecisely and information cannot be adequately processed. This is one of the reasons why movement coordination of muscles cannot be performed correctly by an indivduum with basal ganglia dysfunction. This happens very early in emerging HIV-1-associated encephalopathy so that motor tests are the adequate method for diagnosis. Rapid finger movements have the advantage that no muscle mass has to be moved so that the course of such rapid movements perfectly describes the function of antagonistic muscle groups with a broad cerebral representation. Neuroadiological methods—applied in parallel—may visualize the basal ganglia dysfunction. Perhaps, HIV-1 irritates dopaminergic receptor function in basal ganglia cells. This has to be examined in further neuroradiological (SPECT or PET), virological and molecular-biological studies.

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Peripheral neuropathies associated with HIV and antiretroviral therapies

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Neuromuscular disorders are the most frequent of the neurological complications that occur in association with HIV infection and AIDS. Over one third of patients with AIDS have clinical evidence of peripheral neuropathy. The increased lifespan of HIV-infected patients will likely increase the prevalence of these complications. However, neuromuscular disorders are frequently misdiagnosed, particularly by non-neurological clinicians. Severe systemic disease or central nervous system abnormalities may mask the symptoms and signs of peripheral neuropathy or myopathy.

The type, frequency, and mechanisms of peripheral neuropathies in HIV infection vary with the stage of immunosuppression. Additionally elevated HIV viral load is associated with increased risk and severity of peripheral neuropathy. The use of certain nucleoside analogue antiretroviral agents, specifically didanosine (ddI), zalcitabine (ddC) and stavudine (d4T), may be limited by peripheral nervous system (PNS) toxicity. It is speculated that nucleoside-related toxic neuropathy is caused by mitochondrial toxicity. A recently described syndrome of rapidly progressive "ascending neuromuscular weakness," associated in some patients with elevated serum lactate level and nucleoside therapy (particularly d4T), will be discussed.

Therapeutic strategies for peripheral neuropathy include pathogenesis-based treatment to reverse the underlying mechanism, and symptomatic therapy, primarily for pain. This talk reviews the spectrum of neuromuscular manifestations associated with HIV-infection, neurotoxicity of antiretroviral agents, treatment strategies and clinical trials available for these complications. New directions in research will be presented.