S1

NATURAL RESISTANCE TO HIV INFECTION AND PATHOGENESIS. Jay A. Levy, M.D., Department of Medicine and Cancer Research Institute, University of California, San Francisco, School of Medicine, San Francisco, CA 94143-1270

All infectious diseases have individuals who appear resistant to the infection or survive without symptoms of the infection. HIV is not an exception. Some people can avoid infection by HIV because they lack expression of an HIV co-receptor (e.g. CCR5) on the cell surface. Other modifications in co-receptor expression can affect progression to disease. Importantly, those individuals, who have survived for more than 10 years without symptoms and maintain a healthy immune system, have a cellular immune response, primarily mediated by CD8+ cells that inhibit HIV replication. These CD8+ cells suppress virus production by infected cells without killing the cells. This noncytotoxic response is mediated at least in part by a CD8+ cell antiviral factor, CAF. This novel factor, which lacks identity to any known cytokine or chemokine, blocks virus replication at transcription. The CD8+ cell antiviral response correlates directly with a healthy state; loss in this activity is associated with progression to disease. In addition, some individuals who have had multiple exposures to HIV through intimate sexual contact with infected partners or sharing of needles are not infected. The CD8+ cells from these uninfected individuals also show the antiviral non-cytotoxic immune response. Induction of this type of cellular immune activity would appear important for prevention of HIV infection and, if infection has taken place, resistance to disease progression.

S2

THE EFFECTS OF HAART AND THE COMPARISON OF RISK GROUPS FOR HIV-RELATED NEUROLOGICAL DISEASE

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Now at the beginning of the third decade of the HIV epidemic there are emerging new issues regarding its effect on the brain, these include the effects of highly active antiretroviral therapy (HAART) and an assessment of the influence of risk group on brain pathology. It is known that HIV brain infection results neuropathologically in a range of inflammatory disorders, synaptic/dendritic damage and neuronal loss. Clinically cognitive impairments can develop and these appear to be associated with the neuronal damage and loss. A few years ago, the medical treatment of individuals with HIV disease was revolutionised by the introduction of HAART. However, while the effectiveness of HAART in dramatically reducing plasma viral load has been demonstrated, the ability of these agents to penetrate and be active in the nervous system has yet to be established. Investigation of brain efficacy is a difficult area as it is not accessible before death. Consequently, we are confined to surrogate markers, such as change in cognitive abilities, estimation of drug levels in the cerebrospinal fluid, and assessment in tissue culture models. The current state of our understanding of the efficacy of antiretroviral agents will be discussed. Similarly, investigations of intravenous drug users (IVDs) infected with HIV have revealed that brain pathology also varies between risk groups. Studies that have compared findings in the brain of IVDs and gay men will be presented together with a discussion of the consequences of these findings and the need for investigation of other risk groups.
S3

Chemokines and Apoptosis in HIV Dementia - F. Gonzalez-Scarano, University of Pennsylvania, Philadelphia, USA

The discovery that members of the seven-transmembrane domain chemokine receptor family serve as coreceptors for HIV-1 entry was a seminal discovery that has begun to explain the molecular mechanism behind many phenomenological observations. For example, microglia and brain macrophages, which bear the primary burden of HIV infection in the brain, express several chemokine receptors that serve as coreceptors, including CCR5, CCR3, CXCR4, and perhaps others. The high levels of CCR5 in these cells explain the predominance of CCR5-using strains in the brain. Furthermore, microglia do not require differentiation before they can be infected, again due to the expression of this coreceptor at the cell membrane even during the G0/G1 state. Particularly efficient use of CCR5 in the face of low levels of CD4 expression (which is typical of microglia) may be associated with giant cell formation in the brain. Similarly, expression of chemokine receptors, particularly CXCR4, on neuronal cell surfaces has been associated with neuronal apoptosis after treatment with chemokines. These experiments could provide an additional mechanism through which inflammatory reactions are deleterious to neurons. Neuronal expression of CXCR4 may also be a component of gp120-mediated neuronal abnormalities, since it is conceivable that gp120 from selected HIV-1 strains could bind neurons through CXCR4 absent its primary receptor, CD4, which is not expressed by neuronal cells. In this regard, lack of expression of CXCR4 has been associated with abnormal neuronal migration in the cerebellum of fetal mice. However, CXCR4 expression in human neurons may be delayed until childhood, pointing out potential difficulties in the interpretation of some experiments that cross species boundaries.

S4

HIV-related Peripheral Neuropathies and their Treatment

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In the 15 years since the first descriptions of a novel sensory neuropathy associated with AIDS, advances have been made in defining its epidemiology, clinical and neurophysiological features, and neuropathology. The risk factors and potential determinants for neuropathy have been examined through large ongoing cohorts of HIV-infected individuals. In addition to a sensory neuropathy associated with HIV infection, neuropathy as a toxic effect of dideoxynucleoside use is increasingly common. Biopsy and autopsy studies have defined the neuropathy as a "dying-back" axonopathy, with prominent macrophage infiltration, and a loss of distal nerve fiber terminals. Punch skin biopsy has been developed as a useful technique to demonstrate this loss of unmyelinated fibers. Nerve fiber regeneration is strikingly absent, and unregulated macrophage activation has been hypothesized as one of the critical mechanisms inducing axonal damage and degeneration. There are important parallels between the pathophysiological mechanisms in the peripheral and the central nervous system. Several clinical trials have now been completed, including a large Phase II trial of nerve growth factor which had positive effects both on neuropathic pain and the neurological examination.

S5

CNS INFLAMMATION AND ITS ROLE IN HIV DEMENTIA. V.Hugh Perry, CNS Inflammation Group, School of Biological Sciences, University of Southampton, Southampton, SO16 7PX, UK

The discovery in the mid-1980's that HIV-1 infection of microglia in the brain could give rise to a dementing disease has had a profound influence on the way in which we view inflammation in the brain. It is clear that the microglia, the resident macrophages of the CNS, when inappropriately activated by HIV-1, secrete viral products and inflammatory mediators that can cause in the long term dysfunction and degeneration of neurones. These observations have led to a marked increase in interest in the role that activated microglia might play in injury and diseases of the nervous system as diverse as stroke, trauma, multiple sclerosis, HIV dementia and Alzheimer's disease. These different insults to the brain provoke very different inflammatory responses and this lecture will highlight aspects of inflammation that appear to be unique to the CNS microenvironment.

S6


A variety of HIV-induced lesions of the central nervous system (CNS) have been described including HIV encephalitis, HIV leukoencephalopathy, axonal damage, and diffuse polymyelodystrophy with neuronal loss of variable severity which was shown to result, at least partly, from an apoptotic process. However, no correlation could be established between these changes and HIV dementia (HIVD). From the study of our series of HIV infected patients, it appeared that neuronal apoptosis is probably not related to a single cause. Microglial and glial activation, directly or indirectly related to HIV infection, plays a major role in its causation possibly through the mediation of oxidative stress. In our patients with full-blown AIDS, this mechanism seemed predominant in the basal ganglia and correlated well with HIVD. Axonal damage, either secondary to microglial activation, or to the intervention of systemic factors also contributes to neuronal apoptosis. In pre-AIDS cases, occasional apoptotic neurons were identified suggesting that neuronal damage is an early event. In patients with long lasting HIVD resisting to tri-therapy, there was massive neuronal apoptosis with cerebral atrophy and minimal inflammation. We conclude that, although massive neuronal loss may be responsible for HIVD, neuronal apoptosis is certainly a late event and does not represent the main pathological substrate of HIVD. This more likely reflects a specific neuronal dysfunction resulting from the confluence of several etiopathogenetic mechanisms, some of which may be reversible.

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VIRAL CHARACTERISTICS IN THE CNS. Ting-Huei Wang, Jeanne E. Bell, P. Simmons, Laboratory for Clinical and Molecular Virology and Department of Neuropathology, University of Edinburgh, Edinburgh, UK.

This presentation will review the evidence for the existence of specifically neurotropic variants of HIV-1 that may pre-dispose towards the development of HIV encephalitis (HIVE). Most studies to date have found evidence for genetic separation of HIV populations infecting brain and lymphoid tissue. Genetic differences are most consistently detected in the V1/V2 and V3 hypervariable regions of the env gene, which contain determinants of cellular tropism and cytopathology. However, whether these differences lead to adaptive changes for replication in lymphoid and non-lymphoid cell types, or lead to other biological differences between tissue populations remains largely untested experimentally. What data is available indicates that brain variants use the CCR5 co-receptor for entry into cells, but are generally similar in replication and cellular tropism to variants recovered from lymphoid tissues.

We have recently developed a method to isolate functional env sequences from different autopsy tissues, and in collaboration with Paul Clapham, Chester Beatty Laboratories, ICRF, to investigate their biological properties through the use of pseudotypes. The avoidance of recombination and mis-incorporation errors during PCR provides us with env clones that may preserve specific adaptive changes for replication in CNS cell types that have been lost in the relatively crude attempts at characterisation carried out to date. Through both genetic and biological comparison we have evidence that individuals with HIVE also show extensive macrophage-borne infection in other non-lymphoid tissues, such as the gut, with viral populations resembling those in the CNS. This suggests that HIVE is a specific manifestation of a more general in vivo macrophage tropism of particular strains of HIV, and points to a commonality in the mechanism of infection in these different tissues.

Abstracts

VIRAL PROTEINS AND THEIR ROLE IN HIV-RELATED NEUROPATHOGENESIS

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Depletion of specific neuronal populations in brain and CD4+ T cells in blood and lymphoid tissues is the central problem in acquired immunodeficiency syndrome. Cell loss and apoptosis of these cell types predominantly occurs in infected or "bystander" cells. Proteins encoded by the HIV genome when present intracellularly may either regulate viral gene expression, form structural components of the virus or may possess anti-apoptotic properties. However upon release into the extracellular space several of these proteins have been shown to cause functional impairment or toxicity of brain cells and lymphocytes. This phenomenon of viral protein induced cytotoxicity although best studied in HIV infection is not restricted to this virus and had been demonstrated with several other animal viruses. HIV proteins implicated in neurotoxicity can be found in blood, cerebrospinal fluid and brain tissue. Some of these proteins may readily cross the blood brain barrier and additionally participate in disruption of the blood brain barrier. Each of the viral proteins has some unique property by which they interact with various cell types. But collectively they cause endothelial cell dysfunction, glial cell and macrophage activation, production of cytokines, chemokines, altered glutamate transport and cause excitatory amino acid receptor activation leading to neurotoxicity in select neuronal populations. These proteins may act synergistically with one another or with other neurotoxic compounds such as glutamate and drugs of abuse to cause neurotoxicity. Further, only a transient exposure of these proteins is necessary to initiate a cascade of events that may self perpetuate for several days leading to demyelination of cerebral function. Thus neuroprotective therapies aimed at common pathways of destruction initiated by the viral proteins are essential in addition to antiretroviral therapy to treat/prevent dementia caused by infection with HIV.