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Meeting report

NeuroAIDS, current understanding and future directions

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Recently, the National Institute of Mental Health (NIMH) and the National Institute of Allergy and Infectious Diseases (NIAID) co-sponsored a workshop entitled 'Neuro-AIDS: Approaches for Pathogenesis-Based Therapies'. The fundamental goal of the workshop was to advance the translation of research findings that are relevant to promising therapeutic strategies for nervous system complications of HIV infection from the laboratory to the clinic. In addition, the NIMH sought expert opinion to assist in identifying avenues of research most likely to increase our understanding of the mechanisms underlying the neurobehavioral complications of HIV infection. This information will help define a blueprint for future neuroAIDS research.

The workshop was divided into three sessions in which pertinent questions drafted prior to the workshop served as points of discussion. The sessions focused on: (1) direct effects of the virus on the brain; (2) indirect mechanisms of HIV associated central nervous system (CNS) disease; and (3) tools to assess disease pathology and targeting of potential therapy. The following is an overview of the discussions that took place during the sessions. An effort has been made to summarize, first, what the participants agreed were well-established findings, and, second, the areas of research that should receive increased attention in the immediate future to identify the mechanisms underlying the neurobehavioral complications of HIV infection, and target appropriate therapies.

Significant effort was initially devoted to discussing the concepts of encephalitis and encephalopathy in the context of HIV infection. HIV encephalitis is defined as viral infection of the brain. Definitive diagnosis requires histologic identification of microglial nodular inflammation with multinucleated giant cells, or identification of intra-CNS virus burden by immunocytochemistry or *in situ* hybridization. Because the ability to assess accurately the presence of HIV in the brain prior to examination at autopsy is currently not possible, a diagnosis of HIV encephalitis can only be made by post mortem neuropathological examination. The neurobehavioral complications of HIV infection, initially identified as AIDS dementia complex and later called HIV-1 associated cognitive/motor complex or HIV-1 associated progressive encephalopathy of childhood, are the clinical syndromes resulting presumably from HIV encephalitis. However, a causal relationship between HIV encephalitis and HIV encephalopathy has not been established. Therefore HIV encephalopathy is a clinical diagnosis defined here as the motor and/or cognitive deficits that occur as a result of HIV infection, with no other identifiable opportunistic infections present.

Direct effects of the virus

It was established more than 10 years ago that HIV invades the CNS, and subsequent studies have shown that HIV can be found in the CNS within weeks following infection. Although it is generally agreed that the presence of HIV within the brain is a necessary albeit not sufficient contributing factor for HIV-induced motor/cognitive dysfunction, a causal relationship between the presence of virus in the brain and the occurrence of the neurobehavioral abnormalities has yet to be determined.

However, data are conclusive that the principal cell productively infected by HIV-1 in the CNS is the macrophage/microglia. A restricted, persistent infection of astrocytes as well as infection of endothelial cells of the blood brain barrier (BBB) have also been demonstrated, but the frequency of these observations and their relationship to encephalopathy remain controversial yet under continuing investigation. Neurons and oligodendrocytes are likely not infected.

Overt neuropathological changes are not observed in all patients with HIV dementia. One study reported that multinucleated giant cells and diffuse myelin pallor were specific for HIV-associated

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dementia (HIVD). However these are relatively insensitive markers for the clinical syndrome, and some patients with severe HIVD may not show these neuropathologic abnormalities. These findings support the hypotheses that indirect mechanisms of neuronal dysfunction underlie the pathogenesis of HIVD. In contrast, another study reported that all HIVD patients had severe HIV encephalitis as assessed by measurements of intra-CNS virus burden, but not all patients with HIV encephalitis had clinical histories of dementias. These findings have been interpreted to mean that HIV encephalitis must exist for a period of time before the clinical symptomatology develops. The presence of HIV in the brain prior to the onset of dementia may suggest a causal relationship between virus and clinical dementia. Therefore, cohorts of patients followed during life and examined by autopsy are important and necessary to provide the data to resolve this issue. The development of new approaches to assess CNS virus burden in living HIV$^+$ individuals is critical.

Both direct and indirect effects of the virus on the cellular components of the CNS must be examined to determine the specific alterations in neuronal function that are responsible for resulting motor and cognitivie dysfunction. Assessment of subcortical neuronal damage is needed to confirm or disprove the association of neuronal loss with dysfunction, since this has been previously measured primarily in cortical areas. If confirmed, it will be important not only to identify the mechanisms responsible for neuronal death, but also to determine whether preventing neuronal death will prevent or ameliorate dementia.

Indirect mechanisms of HIV-induced CNS disease

Because a correlation between viral load, neuropathology, and clinical encephalopathy is not universally accepted, a number of investigators have studied the indirect mechanisms that may contribute to HIV-associated CNS dysfunction. One approach has been to evaluate the potential toxicity of specific viral proteins for neurons or other CNS cells. An example is the neuronal toxicity associated with HIV-gp120. The presence and abundance of gp120 in HIV-infected human brains must be determined. Additional studies extending and corroborating the specific effects of gp120 on neurons, both direct and indirect, and potential mechanisms by which gp120 mediates a toxic effect are also necessary.

Other possible factors that may contribute to the occurrence of HIV-encephalopathy include alterations in neurochemical and/or immunochemical parameters that may result from infected macrophages/microglia, astrocytes, or endothelial cells of the BBB. Infection of BBB endothelial cells (EC) by HIV and by SIV in the non-human primate has been reported. However, the incidence of EC infection in humans, determined at autopsy, is rare, and the question of the relevance of EC infection to CNS disease remains controversial. A number of other important unresolved issues remain concerning the role of the BBB in HIV encephalopathy. For example, infected brain capillary EC may represent an important means of seeding the CNS with virus. Alternatively, structural damage to the BBB without actual viral infection of EC may contribute to HIV neuropathogenesis. For example, an MRI study to assess changes that reflect breakdown of the BBB indicated that 11/11 HIV$^+$ demented patients had evidence of BBB breakdown, whereas only 2/11 HIV$^+$ non-demented patients had similar changes. However, abnormal opening of the BBB may not cause dementia, but may in fact be a result of the same pathology responsible for the dementia. The loss of the integrity of the BBB may allow the passage of molecules from the periphery into the brain to alter neuronal functions. If so, what is the nature of those molecules?

Other indirect mechanisms that could be responsible for CNS dysfunction include elevated expression of cytokines or neurotoxins associated with inflammation. Quinolinic acid (QUIN), an endogenous neurotoxin produced by activated or infected macrophages, has been implicated in HIV-induced motor/cognitive dysfunction in both HIV-infected adults and children, and SIV-infected rhesus monkeys. It has been reported that elevated CSF-QUIN correlates with severity of immune deficiency as well as neurological symptoms. A number of inflammatory cytokines, including tumor necrosis factor α (TNF-α), interleukin 1β (IL1-β), transforming growth factor-β (TGF-β), and interferon γ (IFN-γ), are elevated following HIV infection. These cytokines elicit numerous effects with the potential to contribute to CNS dysfunction. These effects include alterations in the expression of cell adhesion molecules, changes in voltage dependent calcium channel currents and stimulation of astrocytosis, as well as alterations in neuronal chemistry. Other potential neurotoxins, including nitric oxide (NO), platelet activating factor (PAF) and eicosanoids, are increased following immune activation such as occurs during HIV infection and could contribute to neuronal injury.

It is likely that a combination of related and interactive factors contribute to the indirect effects of HIV infection on the CNS. If so, identifying and blocking one or more factors may be sufficient to interrupt the cycle of neurologic damage. Definitive evidence is needed to identify specific factors as causal. The SIV infected rhesus model for AIDS dementia is critical in establishing the identity of

the altered parameters contributing to the CNS impairment. As these factors are identified, small, 'proof of concept' clinical, trials should be carried out to validate specific approaches. Assessment of relevant parameters must be implemented with human material as well as with relevant animal models.

Tools for assessing disease pathology and targeting potential therapy

The ultimate goal of understanding mechanisms responsible for HIV-induced CNS disease is to develop therapeutic interventions to prevent the occurrence or to reverse the effects of HIV infection on motor and cognitive function. Inherent in this is the ability to identify the dementia early in disease progression and/or predict the probability of occurrence.

Although preliminary evidence suggests that changes in the neuropsychological assessment, accruing prior to late stage disease, effectively predict the onset of dementia, more evidence is required to firmly support this hypothesis. Functional and structural imaging studies have documented regional loss of CNS tissue in HIV-infected individuals. Definitive studies are needed to elucidate the predictive value of neuroimaging for neurocognitive deterioration and correlation with neuropsychological and other clinical measures.

The importance of animal models to identify pathogenic mechanisms as well as for testing of potential therapeutics was well recognized. There was also strong consensus that models using human cells or tissues grown in immunosuppressed animals and primary cultures are essential and should be emphasized. The importance of using human post-mortem tissues for confirmation of pathogenic mechanisms underlying the documented dysfunction was agreed to be an important need. However, in order to understand the pathogenic mechanisms of HIV-1 infection which are demonstrated in post-mortem tissue, more emphasis must be directed to basic investigations using animal and cell culture models. Also, the difficulty in obtaining human tissue, in particular appropriately preserved tissues from HIV^+ individuals with well-documented disease history, is recognized. A number of research centers, particularly those associated with hospitals with AIDS clinics, have a variety of blood, tissue, and CSF specimens stored that could be made available to researchers upon request. A coordinated effort to catalog and distribute available tissue as well as disseminate information regarding sample availability would assure improved access to this underutilized resource and foster collaborative work.

A number of other hypotheses were addressed which would benefit from new and improved tools for assessment. For instance, better quantitative measures of neuronal injury/death would help to resolve the extent to which cell death contributes to CNS dysfunction. Models reflecting chronic rather than short term neuronal injury may address the question of whether dementia results from subtle neuronal abnormalities accumulating over time rather than an acute crisis, which may in fact occur once a threshold of neurological changes has been reached. New applications of existing techniques are needed to assess altered neuronal physiology and to determine the nature of the neurochemical profile of HIV-infected individuals that may ultimately result in neuronal damage and death. Finally, an increased understanding of T cell and macrophage trafficking into and out of the CNS, including information about adhesion molecules, would serve to elucidate the potential role of infected T lymphocytes as an additional source of cell-associated virus entering the CNS along with HIV-infected monocytes/macrophages.

Neurologic complications of HIV infection represent a serious problem affecting the quality of life in a significant proportion of infected adults and children. Substantial evidence has accumulated over the past few years concerning the nature of the neurological and neurobehavioral complications of HIV infection. The types of motor and cognitive impairments that occur have been determined, and the methods for assessing these impairments continue to be improved. The neuronal pathology associated with HIV infection at end stage disease has been described and efforts to correlate these changes with observed dysfunction during life continue. Definitive identification of the mechanisms responsible for CNS dysfunction will ultimately influence the timing and nature of optimal therapies. A need exists to dissect the particular neurobiological alterations that are associated with the presence of HIV in blood as well as the CNS compartments, and the immunological changes that result from systemic infection. This is a particularly important problem now as new and more potent antiretrovirals are in development that dramatically reduce plasma viral burden. Although decreasing systemic viral load may improve CNS symptoms initially, long term suppression of virus replication may in fact result in HIV infection becoming primarily a CNS disease. This is particularly true in some children, where the systemic disease may be controlled, but in whom severe HIV encephalopathy results in major lifetime handicaps. Prevention or effective treatment of HIV infection of the CNS must be aggressively pursued to reduce morbidity and improve daily functioning of persons living with HIV.

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