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Proceedings of a Workshop on Metabolic Disorders in the Pathogenesis of Nervous System Damage In HIV-Infected Drug Abusers

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In the United States, drug use has been associated with a significant risk of HIV infection, accounting for approximately a third of all cases of AIDS in adults and children. Neurologic disease as a result of HIV infection occurs in a large percentage of infected individuals. In general, these abnormalities occur later in HIV infection, at a time when the individuals manifest significant immunosuppression. As a consequence of both drug use and infection with HIV, neurologic abnormalities can occur that can independently cause significant impairment of function and, synergistically, may potentially act to cause more rapid progression of neurologic disease. To address this issue, a workshop entitled “Metabolic Disorders in the Pathogenesis of Nervous System Damage in HIV-Infected Drug Abusers” was held on September 28–29, 1999, sponsored by the National Institute on Drug Abuse (NIDA). The meeting included presentations from neurologists, neuroscientists, and infectious disease and drug abuse experts, who discussed the potential interactions between drugs of abuse and HIV infection that affect the clinical presentation and course of neurologic symptoms in infected individuals.

Dr. John Brust of Columbia University provided operational definitions of psychic and physical dependence, tolerance, addiction, and abuse and then proceeded to give an overview of the drugs of abuse that are used by illicit drug users. The members of the different classes of abused drugs can have effects that vary depending on the category of drug that is used (e.g., opiates such as heroin and stimulants such as cocaine) and by route of administration (euphoria or sedation vs. the “rush” that occurs with oral and parental opiates or heroin, respectively). These primary pharmacologic manifestations, in concert with symptoms of overdose or withdrawal, and secondary manifestations such as infection, seizures, stroke, and peripheral nerve and muscle complications can easily obscure the clinical picture in patients with impairment caused by HIV infection.

Karl Goodkin, M.D., Ph.D., presented his research discussing the etiology of minor cognitive motor disorder (MCMD) in HIV-infected cocaine users. MCMD has to date been a poorly understood syndrome for which the risk factors have not been clearly identified, and, therefore, effective therapies for treating this syndrome are lacking. Dr. Goodkin and his group have demonstrated that the MCMD may be related to lifetime cocaine use, and that the risk of developing MCMD is modified by the HIV serostatus of the individual.

Studies involving HIV-infected drug users in Edinburgh, Scotland were presented by Jeanne Bell, M.D. This cohort of participants has been followed since the time of seroconversion of its earliest members and has been the subject of numerous informative investigations. Among the data presented were observations that inflammatory infiltrates can appear in the brain early after seroconversion and that, independent of HIV infection, drug use was associated with activation of microglia.

Howard Gendelman, M.D., presented data demonstrating that altered metabolism in the macrophage causes the release of a number of soluble factors that create a microenvironment that is toxic to neurons and glia. In performing these studies, his laboratory has applied precise quantitative techniques for assessing the metabolic state of mononuclear phagocytes and the effects of the secreted factor on neuronal function and integrity.

The role of the neuronal death-related protein, Par-4, was discussed by Mark Mattson, Ph.D., of the University of Kentucky (Dr. Mattson is currently at the NIDA Bay-view campus). His laboratory has observed that HIV Tat induced the production of Par-4 at hippocampal synaptic terminals, suggesting that cognitive and motor abnormalities in HIV infection may be associated with synaptic damage.

Avindra Nath, M.D., also of the University of Kentucky, presented data that demonstrated that damage to dopaminergic neurons could be induced by subtoxic amounts of gp120 and tat in the presence of otherwise benign concentrations of cocaine and methamphetamine (MA). Similar results were obtained when the cocaine and MA were substituted with morphine. The cocaine/MA effects could be inhibited by estrogen, and effects resulting from morphine exposure were blocked by naloxone. Further studies employing currently accepted animal models of neurotoxicity were recommended.

Adrian Dobs, M.D., of the Johns Hopkins University, discussed metabolic and endocrine abnormalities that occur in the context of HIV infection, including the effects and causes of lipodystrophy, alteration of normal lipid metabolism and hyperinsulinemia induced by protease inhibitors; endocrine complications of HIV/AIDS, and various intervention modalities.

Robert Donahoe, Ph.D., of Emory University, has been studying the immune effect of opiates and cocaine in the primate model of SIV infection. In these studies, disease progression associated with opiate administration appears to be dependent on frequency and dose of administration. His investigations highlight the importance of this animal model and the need for its continued development to gain information regarding consequences of drug use in the context of HIV infection.

Gail Shor-Posner reviewed results of her studies demonstrating that antioxidant and selenium deficiency are associated with more rapid progression of cognitive impairment and that repletion of these and, in some cases, other nutrients (e.g., pyridoxine and cobalamin) can lead to significant clinical improvement. The administration of selenium appears to specifically suppress production of TNF- α and IL-8, cytokines which promote increased replication of HIV. Therefore, future studies could address specific mechanisms by which micronutrients may regulate the course of HIV infection in individuals with nervous system impairment.

Finally, the neuroendocrinologic effects of HIV infection were discussed by Mahendra Kumar, Ph.D., who previously showed that infection was associated with abnormal responses to the cold-pressor challenge, which tests hypothalamic-pituitary axis (HPA) function. In his presentation, it was speculated that the reasons for the abnormal function of this system might include the effects of viral proteins, cytokine effects, and metabolic abnormalities that can be induced by specific antiretroviral drugs.

The meeting presenters discussed the evidence that metabolic factors play a significant role in neurologic disease among HIV infected drug users, and concluded that research in the following areas is required to further define associated mechanisms of disease and modalities of treatment in drug abusers.

FUTURE RESEARCH

Metabolic Disorders in the Pathogenesis of Metabolic Disorders in the Pathogenesis of Nervous System Damage In HIV-Infected Drug Abusers

1. Development of a brief neuro-AIDS clinical rating scale that combines assessments that can identify abnormalities which can occur specifically secondary to drug use (e.g., motor abnormalities that result from basal ganglia involvement) with tests that are useful for identifying abnormalities that also occur in other risk groups.
2. Development of drug user cohorts that reflect regional differences in drug use patterns and behavior, realizing that these factors may potentially change over time.
3. Support of infrastructure for making available animals for performing in vivo and in vitro studies of SIV infection.
4. Development of surrogate markers for nervous system involvement in drug users. This would include techniques such as magnetic resonance spectroscopy.
5. Identification of common and unique immunologic and pathologic mechanisms that are important in the pathogenesis of HIV related neurologic disease in drug users.
6. Drug development.
7. Elucidation of neurotransmitter abnormalities.
8. Examination of neuroendocrine effects (HPA, autonomic disturbances).
9. Examination of the role of oxidative stress.
10. Modulation of viral replication in brain by drugs of abuse.
11. Examination of neuroimmune mechanisms.
12. Determination of the effects of age, gender, ethnicity, and genetics on the risk of developing neurologic complications and on the course of the nervous system disease.