

NATAP FORUM

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The Brain, HIV, and the Effect of New Treatments

by Dr. Justin McArthur, MBBS, MPH (given January 17th, 1998)

Neurologic involvement, with both peripheral and central nervous system (CNS) manifestations, is frequent in human immunodeficiency virus (HIV) infection. Such involvement reflects the direct effects of HIV infection and the consequences of cellular immunodeficiency producing opportunistic infections. Human immunodeficiency virus-associated dementia (acquired immunodeficiency syndrome [AIDS]-dementia complex) develops in 15% to 20% of the individuals with AIDS, usually with or after other AIDS-defining illnesses. The incidence of HIV dementia may have declined in the era of highly active antiretroviral therapy. However, because only a few available antiretrovirals penetrate the CNS adequately, the role of the brain as a sanctuary for HIV persistence is becoming increasingly important. Markers or risk factors for development of HIV dementia include anemia, older age, lower CD4 count, and higher plasma viral load. Recently, researchers have found that cerebrospinal fluid (CSF) HIV RNA levels correlate with the severity of neurologic deficits in HIV dementia and with CSF markers of immune activation. It is hoped that CSF viral load will become a useful tool to monitor the effects of HAART on HIV dementia. Clinical trials are underway with CNS-penetrating antiretrovirals.

In this program, the diverse range of neurologic complications of HIV infection will be described, focusing on HIV-associated dementia. Techniques for detecting and monitoring the effects of therapy on HIV dementia, as well as recent studies of the relationship between neurologic deficits and plasma and CSF HIV levels, will be reviewed.

1. Introduction to neurologic disease

Before HIV was identified as the cause of AIDS, a variety of opportunistic infections involving the CNS were described. The severe disruption of cellular immunity permitted reactivation of latent infections (eg, toxoplasmosis) or development of truly opportunistic precesses (eg, cryptococcosis) (endnote 1). Eventually it became evident not only that neurologic disorders were common in patients with HIV infection, but that some of these conditions could not be ascribed to opportunistic processes and appeared to represent novel conditions (see Table 1).

Table 1. Neurologic disorders considered to be indicators of AIDS

(Centers for Disease Control and Prevention. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome)

HIV related	Cumul ative prevalence	Opportunistic processes	Cumulati ve prevalence
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Acute aseptic meningitis	1-2%	Cryptococcal meningitis**	approx. 5%
Chronic meningitis	>50%	Toxoplasmosis**	approx. 5%
HIV-associated dementia	15-20%	Cytomegalovirus encephalitis**	3%
Minor cognitive impairment	20%	Tuberculous meningitis	2%
Vavular myelopathy	5-10%	Neurosyphilis	3%
Predominantly sensory neuropathy	20-30%	Herpes group encephalitis	2%
Inflammatory demyelinating polyneuropathy	2-3%	Progressive multifocal leukoencephalopathy**	approx. 5%
Mono neuritis multiplex	1%	Primary CNS lymphoma**	approx. 5%
Myopathy	2%		

* = Cumulative prevalence during HIV infection estimated from CDC data, Johns Hopkins University data, and other sources.

**= AIDS defining illnesses (CDC 1983).

These disorders probable represent the direct or indirect effects of HIV infection on the nervous system. There are important parallels between these human conditions and the animal lentivirus infections, because all lentiviruses cause a degree of neurologic damage (endnotes 2 and 3). The nervous system is involved frequently, sometimes before the development of opportunistic infections and frank AIDS. Surveillance data from the Centers for Disease Control and Prevention (CDC) indicate that in 1994, CNS complications (including HIV encephalopathy) made up 6419 (8%) of all AIDS-defining diseases in the 79,674 patients with AIDS (endnotes 4 and 5).

II. Viral load in HIV dementia

The essential features of HIV dementia (HIV-D) are disabling cognitive impairment, usually accompanied by motor dysfunction and behavioral changes (endnote 6). The

dementia usually progresses quickly, with mean survival of 6 months or less, and most patients succumb to the effects of neurologic disease (endnote 7).

Generally, HIV-D develops with immunodeficiency, and the prevalence of HIV-D is low during the asymptomatic phase of HIV infection, rising to 15% to 20% among patients with symptomatic HIV disease (endnotes 7 and 8). We determined that the annual incidence of HIV-D was 7% after AIDS, and defined markers or risk factors that might identify individuals at higher risk such as anemia, constitutional symptoms, and low body weight before AIDS (endnote 9).

Studies of HIV viral load have largely been limited to its impact on systemic disease, and generally have not focused on neurologic disease. Before the development of quantitative polymerase chain reaction (PCR) techniques, research demonstrated that increases in systemic HIV load, assessed either by p24 antigen or by plasma viremia, correlate with increasing stage of HIV infection. This is associated with progression to AIDS in HIV-seropositives and signifies a poor prognosis (endnotes 10-14). The refinement of quantitation of viral RNA or particle-associated RNA has become a useful tool for monitoring the levels of replicating HIV within an individual patient. Several studies, using either RT-PCR or branched DNA techniques, have demonstrated that viral load monitoring is a powerful predictor of disease progression and clinical outcomes (endnotes 15 and 16). Measurement of viral load, an important component of clinical practice, can serve as a surrogate for clinical endpoints for monitoring systemic therapy for HIV infection.

In infected patients, HIV virions can frequently be detected in CSF, sometimes at very high levels, even in clinically asymptomatic individuals (17 and 18). Chiodi et al found that the presence of CSF viral RNA was independent of the stage of infection or neurologic symptoms (endnote 19). Recently, Conrad et al used a customized PCR assay to detect and quantify CSF and serum HIV RNA (endnote 20). Neurologic dysfunction correlated with serum but not CSF RNA levels. However, using the commercially available Amplicor (Reg. TM) viral load assay, several groups have demonstrated the existence of a significant relationship between CSF viral load and the severity of neurologic disease (endnote 21-23). Such discrepancies in the findings may relate to the severity of neurologic disease or to the sensitivity of the assay. No studies have yet examined CSF viral load with the NASBA (TM) assay or evaluated the relationship between CSF and brain levels of HIV. In our laboratory, we assessed the prognostic ability of HIV RNA levels measured cross-sectionally in CSF, plasma, and brain samples. We examined the relationship between viral load and dementia severity, immune status, and markers of immune activation.

We used the NASBA (TM) assay for the first time to examine the relationship between viral load and neurologic status in 207 clinically characterized HIV-seropositive subjects. After controlling for CD4 count, the levels of CSF HIV RNA were significantly higher among those with HIV dementia, and correlated with a marker of CNS immune activation, CSF Beta2-microglobulin. Plasma HIV RNA levels correlated significantly with CSF HIV RNA levels in patients with low CD4 counts, but this did not distinguish demented subjects from comparably immunosuppressed subjects without dementia.

Tissue levels of HIV RNA in the CNS, which ranged from undetectable to 8.14 log copies per gram, correlated weakly with CSF HIV RNA levels in demented subjects, but not closely with neurologic status.

Our data are consistent with recent work from other investigators, which have shown a very strong relationship between plasma RNA levels and stage of HIV disease (endnote 15). For example, with specimens obtained from the Multicenter AIDS Cohort Study (MACS), Mellors et al found that plasma HIV RNA was a strong CD4-independent predictor of rapid progression to AIDS (endnote 24). The levels of plasma HIV RNA increased 30 to 50 months before AIDS, suggesting that it is an early marker of disease progression. In our cross-sectional analysis, plasma HIV levels did not distinguish demented subjects from comparably immunosuppressed subjects without dementia. However, the strong association between the severity of dementia and CSF viral load suggest that increasing levels of viral replication in the CNS or CSF compartments contribute substantially to neurologic disease.

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Speakers at the January 17th Forum:

Jules Levin, Executive Director of NATAP - Welcoming Address

Dr. Robert Siliciano, MD - HIV in the Lymph Tissue and Latent Long-lasting Virus in T-Cells (CD4s).

Dr. Justin McArthur, MBBS, MPH - The Brain, HIV, and the Effect of New Treatments

Dr. Carl Fichtenbaum, MD - Treatment and Prophylaxis for Opportunistic Infections in the New Potent Therapy Era. Can Prophylaxis or Maintenance Therapy Be

Discontinued?

Dr. Louise Markert, Thymus Transplant Research for HIV and Its Potential for Immune Reconstitution