Neurological Manifestations of HIV-1 Infection in the HAART Era

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INTRODUCTION
Neurologic disease has been a recognized complication of infection with human immunodeficiency virus (HIV) since early in the epidemic of the acquired immune deficiency syndrome (AIDS). Certain patients may develop opportunistic infections and present with typical symptoms of infectious disease such as fever and malaise. The challenge in these patients is localizing the neurological deficit, determining the etiologic agent, and initiating appropriate therapy as early as possible. Others infected with HIV develop primary neurological diseases that are thought to be due to a direct consequence of viral infection of nervous tissue or to indirect mechanisms secondary to viral infection. These include dementia, vacuolar myelopathy and certain forms of neuropathy. (Table 1) Advances in drug therapy have led to the development of effective antiretroviral medications for the treatment of HIV infection, which has had a major impact on the incidence and course of some neurological diseases in the setting of AIDS, but also have inherent neurological toxicities.

OPPORTUNISTIC INFECTIONS/NEOPLASMS
Opportunistic infections of the central nervous system (CNS) in patients with AIDS are numerous and the predilection of specific pathogens is related to defects in cell-mediated immunity. The clinical presentations of these infections are protean and diagnosis rests on a combination of clinical, serologic and cerebrospinal fluid (CSF) tests, neuroimaging, brain biopsy, and response to empirical therapy.

Toxoplasmic encephalitis. Toxoplasma gondii is an obligate intracellular protozoan and the causative agent of toxoplasmic encephalitis (TE). Prior to 1981, TE was generally seen in patients with malig-
nancy or those receiving immunosuppressive drugs for organ transplantation. With the advent of AIDS, TE has increased in frequency, particularly in the later stages of HIV disease and became the most common cause of focal brain lesions by 1988. However, advances in prophylaxis for opportunistic infections such as *pneumocystis carinii* pneumonia, have led to lower rates of TE over the past decade.

Patients with TE generally present with a subacute onset of symptoms. Typical complaints include headache, which may be severe and localized, and neurologic deficits such as weakness, focal sensory complaints, and gait instability. Signs of focal neurologic dysfunction may include: hemiplegia, hemiparesis, dysphasia, movement disorders, diplopia, hemianopsia, cranial nerve palsies, tremor, Parkinsonism, sensory loss, and intractable hiccups. Focal or generalized seizures may herald TE in up to 25% of cases. Focal signs may be accompanied by generalized cerebral dysfunction in the form of confusion or delirium.

Serum antitoxoplasmic immunoglobulin G is insufficient to establish a diagnosis of TE since many healthy individuals harbor latent infection of the organism. However, the absence of antitoxoplasmic antibodies is strong evidence against TE and should prompt the consideration of alternative diagnoses in patients with focal brain lesions. CSF polymerase chain reaction (PCR) for toxoplasmic DNA has a low sensitivity but may be useful to confirm the diagnosis. However, empirical therapy should not be delayed while awaiting results. Magnetic resonance imaging (MRI) is the preferred neuroimaging procedure to identify focal brain lesions in patients suspected of having TE and is more sensitive than computed axial tomography (CT). MRI typically demonstrates multiple ring enhancing lesions. (Figure 1) A focal brain lesion in patients who are seronegative for toxoplasmic antibodies is more likely to represent an entity other than TE, such as lymphoma. In these patients and those with a positive single photon emission computed tomography (SPECT) scan, brain biopsy is recommended to seek alternative diagnoses, especially primary CNS lymphoma. Treatment of TE includes pyramethamine 75 mg daily with folinic acid 20 mg daily and sulfadiazine 4–6 gm daily for up to 6 weeks, followed by lower maintenance doses, usually for the duration of the patient’s life.

**Progressive multifocal leukoencephalopathy.** Initially a rare disease primarily seen in patients with lymphoproliferative disorders and abnormal cell-mediated immunity, progressive multifocal leukoencephalopathy (PML) may be detected in up to 5% of autopsied AIDS patients. The causative agent is a polyomavirus, named JC virus after the first patient in whom it was isolated. Activation of...