Neurology of AIDS Virus Infection:
A Clinical Classification

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Infection with the AIDS virus itself (HIV, HTLV-III, LAV, ARV) is associated with a full
spectrum of neurological disorders. The application of diagnostic studies for HTLV-III infection
has demonstrated that these neurologic disorders can be the first manifestation of AIDS or occur
in the absence of AIDS. The most common conditions associated with HTLV-III infection alone
are a subacute encephalopathy (AIDS dementia) and peripheral neuropathy; however, vacuolar
myelopathy and both acute and chronic aseptic meningitis are also common. Congenital (or
neonatal) transmission of the virus can result in a mental retardation syndrome of delayed onset.

The AIDS virus is neurotropic as well as targeting T-helper lymphocytes. The virus has been
readily identified in neural tissues and cerebrospinal fluid, including instances in which other
central nervous system infections, such as toxoplasmosis, coexist. Hence, recognition of an
appropriate syndrome, neurodiagnostic studies, and exclusion (or treatment) of other infections,
also as evidence for HTLV-III infection are required for diagnosis. The development of
successful therapy will require agents which cross the blood-brain barrier.

The acquired immunodeficiency syndrome (AIDS) virus (HIV, HTLV-III, LAV, ARV) has tropism for both lymphocytes and the nervous system. The acquired immunodeficiency syndrome and the massive opportunistic infections associated with it result from the infection of the T-helper lymphocytes (T4) and their consequent
destruction. The immunodeficiency syndrome in its full-blown and lethal expression is,
however, only part of the disease spectrum. In this review we focus on the clinical
syndromes which result from the effect of the AIDS virus itself on the nervous
system.

It was recognized relatively early that opportunistic central nervous system (CNS)
infections were common in AIDS patients [1]. Apart from the AIDS virus, the most
common cerebral infections have been cytomegalovirus (CMV) and toxoplasmosis
[2,3,4]; however, many other opportunistic infections have been documented (Table
1). Primary CNS lymphoma of B-cell origin [5] occurs, and the role of Epstein-Barr
virus (EBV) in these tumors requires further study [6]. Progressive multifocal
leukoencephalopathy, a condition associated with papovavirus infection of the brain in
settings of impaired cellular immunity, occurs with an increased frequency in AIDS.
Viral encephalitis or myelitis, particularly that caused by agents often seen in the
context of impaired cellular immunity, such as varicella-zoster virus (VZV), are also

Abbreviations: AIDS: acquired immunodeficiency syndrome ALS: amyotrophic lateral sclero-
sis ARC: AIDS-related complex ARV: AIDS-related retrovirus CMV: cytomegalovirus EBV:
Epstein-Barr virus HIV: human immunodeficiency virus HTLV-III: human T-cell lymphotropic virus
III LAV: lymphadenopathy virus VZV: varicella zoster virus

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found. Acute aseptic and chronic meningitis are frequent, with cryptococcus as a common cause of chronic meningitis.

Demonstration of CNS infection by human T-cell lymphotrophic virus III (HTLV-III) was first achieved in the investigation of the subacute encephalopathy of AIDS. The potential cause of this condition, a subacute dementing illness with an inexorable course, was thought to be viral, such as CMV or HTLV-III. Shaw et al. demonstrated the DNA of HTLV-III in the brains of five of 15 cases of AIDS encephalopathy, and viral-specific RNA in four of those five [7]. Furthermore, the quantity of HTLV-III in these brains was sometimes greater than that found in lymphoid tissues. Subsequent studies by Levy et al. [8] and Ho et al. [9] have confirmed the finding of the AIDS virus in the brain and have identified it in the cerebrospinal fluid (CSF). In addition, Ho and his colleagues have found the virus in the spinal cord and in peripheral nerves [9]. In a study of intra-blood-brain-barrier synthesis of antiviral antibody, Resnick et al. concluded that infection of the nervous system by the AIDS virus occurred in the majority of AIDS patients with neurologic symptoms [10]. Hence, there is strong evidence based on several types of data that the virus of AIDS infects the human nervous system. The presence of mRNA for T4 (the AIDS virus receptor) in human cerebral cortex has been reported by Maddon et al. [11]. Other studies, described below, have examined the cell types containing the virus.

With the widespread application of tests specific for the AIDS virus, it has become apparent that many neurologic syndromes are not the result of superimposed infections but result from the AIDS virus itself. While the viral or host defense mechanism(s) responsible for these syndromes remain a topic of intense investigation, their clinical delineation has become clear. All levels of the nervous system can suffer as a direct consequence of AIDS virus infection (Table 2). Brief descriptions of these syndromes follow.

**PROGRESSIVE ENCEPHALOPATHY OF INFANTS**

In a proportion of children with AIDS, the risk factor is use of blood products or transfusions. For the majority of infants two years or younger, particularly for those
less than a year old, however, it is the presence of a risk factor in a parent [12]. This fact raises the possibility that the AIDS virus infection is transmitted transplacentally during gestation or by an infected birth canal [13] at delivery. Such infants are at risk for developing a progressive and ultimately fatal encephalopathy. After a variable period of apparently normal development, loss of motor milestones and intellectual regression occur [14–16]. Pyramidal tract signs, myoclonic jerks, ataxia, seizures, and microcephaly can be observed clinically and cortical atrophy demonstrated on CT scanning. Pathological changes are most frequently found in the basal ganglia, pons, and white matter [16]. Nucleic acid hybridization studies have demonstrated the presence of the viral genome in the brain [7] and electron microscopy has identified retroviral particles in multinucleated giant cells in the brain [16]. The molecular pathogenesis of the progressive encephalopathy of infants and children, however, as in adults, remains unknown.

AIDS DEMENTIA (SUBACUTE ENCEPHALOPATHY)

A subacute dementing process associated with AIDS, variously termed a subacute encephalitis, subacute encephalopathy, or AIDS dementia, is the most common CNS disorder associated with the AIDS virus [17]. It results from infection with the AIDS virus itself rather than from superinfection with another organism [7,16,18]. The onset is most often subtle and difficult to distinguish from other processes which afflict AIDS patients. Thus, apathy, reduced concentration, and impaired recent memory can also result from depression or a metabolic encephalopathy secondary to other organ dysfunction. On occasion, the presentation is more dramatic, with agitation and an apparent acute psychosis. In patients without documented AIDS or AIDS-related complex (ARC), the presence of a risk factor and residence in an epidemic center should raise the suspicion of an AIDS virus-induced dementia. Over a course of weeks to months, patients progressively lose motor function, and become globally demented,
and many experience myoclonus or seizures. In the end stage, such unfortunate individuals are bed-bound, quadriparietic, doubly incontinent, and severely demented.

Early in the course of the dementia, the most important consideration is to exclude potentially treatable infections such as toxoplasmosis infection of the brain or fungal meningitis. Unfortunately, there is no specifically diagnostic test for AIDS dementia. Even identification of HTLV-III in the CSF does not exclude the possibility of the simultaneous presence of another infection. The CT scan may demonstrate atrophy and white matter attenuation. The lumbar puncture often demonstrates a mononuclear pleocytosis and somewhat elevated protein and may contain oligoclonal bands of IgG. Although special studies have demonstrated the production of viral-specific IgG antibody in the CSF [10], such antibody does not exclude the presence of an additional infection. The EEG frequently demonstrates nonspecific bilateral abnormalities. Effective specific antiviral therapy will require the capacity to penetrate the blood-brain barrier.

In addition to the multinucleated giant cell, the principal cell containing the virus in the brain appears to be the monocyte. Several lines of evidence, including immunohistology [18,19], in situ hybridization [19,20], and characterization of cells from which virus has been isolated in vitro [21], demonstrate the monocyte/macrophage to be the principal target. The role of capillary endothelial cells has been emphasized in one study [19]. Less frequently, neurons and glia have evidence of infection [19,20]. Koenig et al., however, combined in situ hybridization and cytochemical techniques to demonstrate that over 93 percent of cells producing viral RNA were of macrophage lineage [22].

**ACUTE ENCEPHALOPATHY**

Many of the syndromes discussed in this review occur in the setting of established HTLV-III infection and represent subacute or chronic responses to persistent infection. Other entities, however, including an acute encephalopathy, appear to result from initial infection with the AIDS virus. Carne et al. [23] have described three patients who experienced a reversible encephalopathy. In two of these patients, seroconversion for HTLV-III antibody was demonstrated at the time of the encephalopathy. The illnesses were characterized by prodromes of fever, malaise, forgetfulness, and personality change. Two of the patients experienced seizures. All recovered from these particular illnesses. This syndrome appears to be quite uncommon, and its mechanism is unknown.

**CEREBRAL GRANULOMATOUS ANGIITIS**

Granulomatous angiitis of the CNS is an uncommon condition resulting in multiple infarcts. It is sometimes associated with evidence of VZV infection. Yankner et al. have reported a case in which no VZV activity was found, and which appeared to result from an early infection with the AIDS virus [24]. Virus was recovered from the CSF and brain biopsy of a 42-year-old homosexual male with a progressive neurologic disorder. Testing for serum antibody to the AIDS virus was negative. Autopsy revealed multiple infarcts of various ages, inflammation of all layers of involved arteries, focal necrosis with fragmentation of the internal elastic lamina, and fibrous internal scarring. Multinucleated giant cells were observed, usually in the region of the internal elastic lamina. The case would appear to represent another early manifestation of AIDS virus infection.
VACUOLAR MYELOPATHY AND OTHER SPINAL CORD CONDITIONS

Petito and her colleagues have identified a vacuolar myelopathy in over 20 percent of a large series of AIDS patients coming to autopsy [25]. Microscopically characterized by vacuolation of white matter in the presence of lipid-laden macrophages, it was most severe in the posterior and lateral columns of the spinal cord. Clinically it is characterized by a progressive paraparesis with spasticity, ataxia, and the development of urinary incontinence. Clinical recognition may sometimes be difficult because of the simultaneous presence of AIDS dementia with its associated impairment of motor function. Thus, 70 percent of cases reported by Petito et al. were demented [25]. This syndrome does not present as a transverse myelitis. If an acute transverse myelitis occurs in an AIDS patient, a thorough search for treatable infections must be made after a compressive lesion has been excluded. For example, varicella-zoster-associated myelitis merits treatment with acyclovir.

A patient has been reported in whom amyotrophic lateral sclerosis and LAV/HTLV-III infection appeared to be temporally linked [26]. Previous studies of a murine retrovirus have demonstrated the experimental induction of anterior horn cell disease in mice [27]. Clinically, the importance of the AIDS virus for motor neuron syndromes is unclear. In another case report, spinal myoclonus with negative spinal CT and MRI studies has been described in an otherwise asymptomatic homosexual man [28]. The CSF contained antibody against HTLV-III. The spinal myoclonus was distinguished from generalized myoclonus, which can be associated with AIDS encephalopathy.

ASEPTIC MENINGITIS

Patients with AIDS and ARC experience aseptic meningitis in a variety of forms. Acute self-limiting [1], recurring, chronic, and complicated forms [29] of aseptic meningitis are encountered. Furthermore, a chronic CSF pleocytosis without meningeal signs can be a worrisome finding in this population. HTLV-III infection can itself be associated with acute aseptic meningitis [9,10] and also with chronic meningitis [9]. It is clearly important to exclude other treatable infections such as fungal meningitis in this population. It is also worth noting that the homosexual male population is at risk for herpes simplex virus (HSV)-II aseptic meningitis and that such cases might deserve a therapeutic trial of acyclovir. Once other treatable processes have been excluded, however, the knowledge that HTLV-III is associated with aseptic meningitis may temper repeated efforts to find other infections if the clinical condition is stable.

PERIPHERAL NEUROPATHY

Progressive distal symmetric sensorimotor neuropathy is common in patients with AIDS or ARC [1,29]. Usually the neuropathy presents with dysasthesias and can progress to sensory loss, distal weakness, and atrophy. Also observed in patients infected by HTLV-III are mononeuritis multiplex, chronic inflammatory demyelinating polyradiculoneuropathy, and acute Guillain-Barré syndrome. Patients with inflammatory demyelinating neuropathies may be seropositive for the AIDS virus but have no clinical evidence of AIDS or ARC [30]. Nerve conduction studies reveal demyelinating patterns, and nerve biopsies demonstrate demyelination and inflammation. CSF proteins are elevated, and a pleocytosis is usually found. It has been reported that patients with chronic inflammatory demyelinating polyradiculoneuropathy benefit from plasma exchange [30,31].
POLYMYOSITIS

Two cases of poliomyelitis in homosexual men have been reported by Dalakas et al. [32]. Serologically positive for HTLV-III antibody, neither patient had ARC or AIDS at presentation but later developed these conditions. Viral antigens were identified in the T4 lymphocytes invading muscle but not in the muscle cells themselves. Both patients were treated with steroids, resulting in significant clinical improvement in one.

CONCLUSIONS

It is important to recognize the clinical patterns of neurologic disease associated with HTLV-III infection. It has become apparent that significant disability, such as the dementia syndrome, can result from HTLV-III infection in the absence of AIDS. Hence, physicians must maintain a high level of clinical suspicion, particularly in epidemic areas, seek the presence of risk factors, and do serologic testing. In light of the continuing increase of the AIDS epidemic in the U.S. and the potential for increased heterosexual transmission, as in Africa, it is likely that the incidence of AIDS virus-related neurologic conditions will continue to increase.

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