

Human Immunodeficiency Virus Type 1 Infection of the Brain

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INTRODUCTION

The *Lentivirinae*

Human immunodeficiency virus type 1 (HIV-1), the causative agent of AIDS, belongs to a neurotropic subfamily of retroviruses known as the *Lentivirinae* (140). The term lentivirus was first used in 1954 by Sigurdsson to describe several infectious diseases that occurred in domestic sheep (338). Members of the lentivirus subfamily include HIV-1, HIV-2, Maedi-visna virus, equine infectious anemia virus, caprine arthritis-encephalitis virus, bovine immunodeficiency virus, feline immunodeficiency virus, and simian

immunodeficiency virus (Table 1) (261). In addition to their neurotropism, the lentiviruses all share the ability to infect cells of the immune system, particularly monocyte/macrophages, and give rise to disease after latent periods of months to years (130-132, 248, 261-264). The lentiviruses can be subdivided into two groups, those that induce immunodeficiency in their hosts and those that do not. The primate lentiviruses (HIV-1, HIV-2, and simian immunodeficiency virus) and the feline immunodeficiency virus belong to the subgroup referred to as immunodeficiency viruses. This group of viruses gives rise to a variety of diseases that result from direct virus multiplication in cells and tissues as well as opportunistic infections that arise as a result of the immunocompromised state of the host. Diseases caused by lentiviruses can be acute or chronic and are often associated

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TABLE 1. The *Lentivirinae*

Species	Natural host	Neurological disease(s)
Maedi-visna virus	Sheep	Chronic inflammatory disease characterized by mononuclear cell invasion of brain
Equine infectious anemia virus	Horse	Hemolytic anemia, mononuclear cell invasion of brain
Caprine arthritis-encephalitis virus	Goat	Chronic inflammatory disease resulting in arthritis and slow progressive neurological disease, encephalitis
Bovine immunodeficiency virus	Cattle	Cachexia and lymphadenopathy, encephalitis
Feline immunodeficiency virus	Cat	Cachexia and lymphadenopathy, increased susceptibility to opportunistic infections, neuropathology?
Simian immunodeficiency virus	Several species of nonhuman primate	Disease similar to AIDS occurring in macaques, evidence of encephalitis
HIV-1	Human	AIDS-associated cognitive-motor complex
HIV-2	Human	AIDS, neurological disease?

with infiltration of the affected organ systems with mononuclear cells. Clinical manifestations of lentivirus infection include glomerulonephritis, hemolytic anemia, hemorrhage, cachexia, and encephalitis. The symptoms and clinical course of disease differ with the different viruses and hosts (Table 1).

Genomic Organization and Life Cycle

Like other retroviruses, the lentiviruses all encode an RNA dependent-DNA polymerase (reverse transcriptase) (*pol*), group-specific antigens (*gag*), and envelope proteins (*env*) (59, 69, 380). However, the genetic organization of

lentiviruses is more complex than that of other retroviruses in that they encode several additional regulatory proteins (62, 69, 72, 79, 277, 306, 312, 317, 320, 344, 353, 386) (Fig. 1A). In HIV-1, these proteins include Tat, Rev, Nef, Vif, Vpu, and Vpr.

Soon after the HIV-1 genome enters a cell, it is reverse transcribed by a virally encoded protein, reverse transcriptase. The double-stranded DNA copy of the HIV-1 genome is translocated to the nucleus, where it integrates into the genome of the infected cell. Transcription of early viral genes results in the production of multiply spliced mRNA species that encode the Tat, Rev, and Nef proteins (69, 70, 183, 286, 312, 347). Unlike Nef, Vif, Vpu, and Vpr,

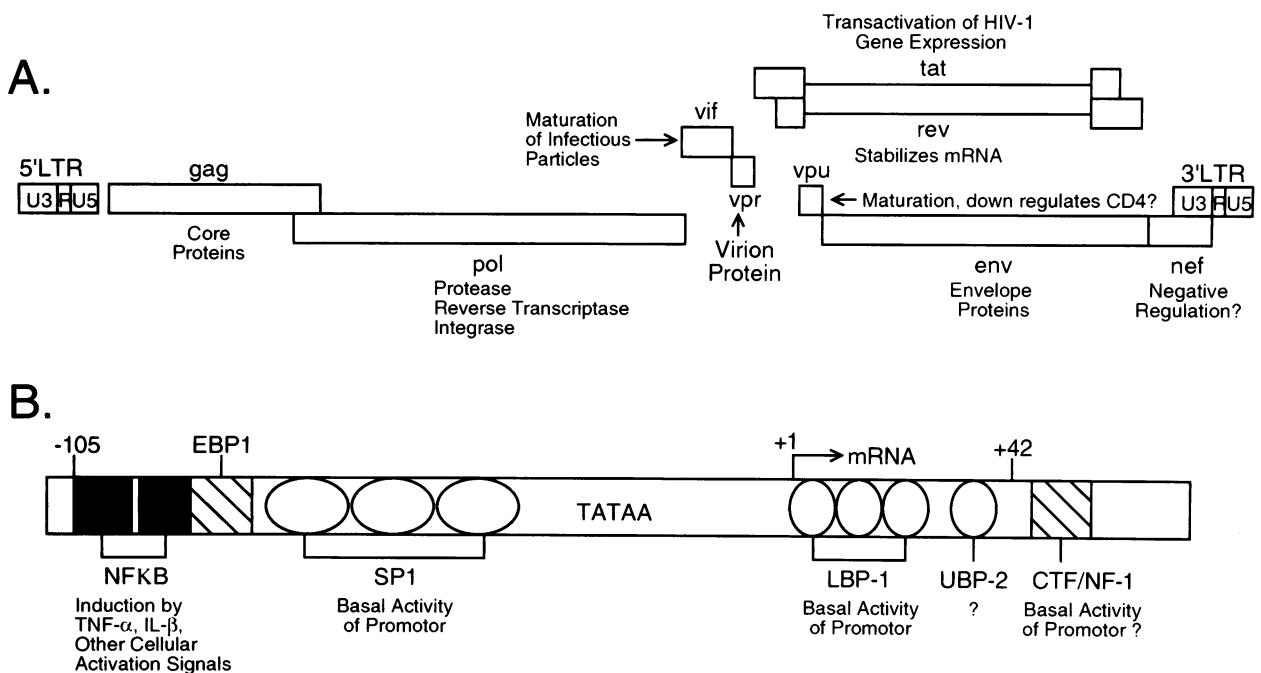


FIG. 1. (A) Genomic organization of HIV-1. The proteins and their known or postulated functions are indicated. (B) Schematic of transcription factors that bind to the HIV-1 LTR. See text for detail and references.

Tat and Rev are essential for HIV-1 multiplication in tissue culture (68–70, 83, 183, 343, 347). Tat functions to increase the expression of multiply spliced mRNAs and hence its own expression and the expression of both Rev and Nef (67, 68, 71, 73, 156, 228, 229, 231). When Rev reaches a critical level, it binds to mRNA via a Rev responsive element and stabilizes the mRNA (74, 77, 109, 124, 222, 229–231, 312, 326–330). This results in a shift from multiply spliced mRNA to singly spliced and unspliced mRNAs. The unspliced mRNA encodes the structural proteins of the virus, Gag and Pol, and the singly spliced message encodes the auxiliary proteins Vif, Vpr, and Vpu. The function of many of the auxiliary proteins is unclear. Both Vif and Vpu have been shown to enhance maturation and release of infectious HIV-1 particles from the cell (62, 70, 352, 387). Recent evidence has shown that expression of Vpu results in degradation of the CD4 glycoprotein (378). Vpr appears to be a particle-associated regulatory protein (60, 61, 277). The role of Nef is not clear. Several groups have reported that Nef has no effect on viral gene expression or replication, while others have reported that Nef negatively regulates gene expression (3, 15, 48, 151, 192, 269). In addition, Nef expression has been correlated with a down-regulation of CD4 expression on the surface of infected T cells and has been shown to inhibit NF- κ B induction of the HIV-1 long terminal repeat (LTR) (123, 269). Recently, the Nef gene was cloned directly from peripheral blood of two HIV-1-infected individuals and inserted into an infectious molecular clone of HIV-1 (87). The presence of the naturally occurring Nef gene was found to accelerate HIV-1 replication in primary human T cells but not in T-cell lines, suggesting that Nef plays an important role in the virus life cycle *in vivo* (87). In addition, Nef mutants of simian immunodeficiency virus have been shown to replicate inefficiently in rhesus monkeys and fail to induce disease in those animals (189).

Several cellular transcription factors are also important in the regulation of HIV-1 gene expression (69, 70, 73, 182, 250, 366, 383). The 5' LTR of HIV-1 contains binding sites for several transcription factors, including NF- κ B, SP1, EBP-1, LBP-1, UBP-2, and CTF/NF-1 (182, 366, 383) (Fig. 1B). The transcription factor SP1 is expressed ubiquitously in cells and has been shown to function in the basal activity of the HIV-1 promoter (155, 182, 284). LBP-1 and CTF/NF-1 have been postulated to function in the basal activity of the promoter. The functions of EBP-1 and UBP-2 are not known. NF- κ B is an inducible transcription factor that is associated with reactivation of HIV-1 from chronically infected cells by phorbol esters and various cytokines, including tumor necrosis factor alpha (TNF- α) and interleukin-1 β (IL-1 β) (14, 186, 209, 260, 361, 366).

Unlike most other retroviruses, the lentiviruses, including HIV-1, do not require dividing cells for multiplication; rather, they multiply in cells that are terminally differentiated or activated (131, 132, 149, 359, 373). Lentiviruses that can replicate in T lymphocytes, however, maintain a requirement for T-cell activation as well as T-cell proliferation.

CLINICAL MANIFESTATIONS OF HIV-1 INFECTION OF THE CENTRAL NERVOUS SYSTEM (CNS)

Acute HIV-1 Meningitis and Meningoencephalitis

HIV-1 enters the nervous system shortly after infection (116, 126, 162, 308, 350). In one case of an iatrogenic infection, HIV-1 was demonstrated in the brain within 2 weeks (80). In the majority of acutely infected persons, entry

of HIV-1 into the brain is either clinically silent or unrecognized, but on occasion an acute meningitis or meningoencephalitis may occur. These illnesses generally develop 3 to 6 weeks after primary HIV-1 infection. Not infrequently, acute neurological complications of HIV-1 infection develop in tandem with an illness resembling infectious mononucleosis and is characterized by sweats, rigors, arthralgias, myalgias, nausea and vomiting, sore throat, abdominal cramps, and diarrhea. Fever, generalized lymphadenopathy, pharyngeal injection, splenomegaly and splenic tenderness, maculopapular rash, and urticaria are observed on physical examination (64, 162). Laboratory studies may reveal transient thrombocytopenia and lymphopenia with an inversion of CD4/CD8 (helper/suppressor) lymphocyte ratio. This acute illness is seldom recognized as a consequence of HIV-1 infection. Furthermore, serological tests for the presence of HIV-1 antibodies are typically not positive during this stage of infection, requiring an average of 8 to 12 weeks from the time of infection for their detection. Transient HIV-1 antigenemia that precedes the development of detectable HIV-1 antibody by 6 to 8 weeks and that lasts 3 to 4 months may be seen with acute infection (143). In addition to measuring HIV-1 p24 antigen, viral culture and the use of polymerase chain reaction to detect HIV-1 provirus may be helpful in diagnosing the HIV-1 infection prior to seroconversion (379).

The meningitis (162, 165) or meningoencephalitis (45) that supervenes is characterized by headache, meningismus, photophobia, generalized seizures, and altered mental state. On rare occasions, other neurological complications may accompany acute HIV-1 infections, including ataxia (33, 323), cranial neuropathies (171), acute meningoradiculitis (285), acute myelopathy (85), cauda equina syndrome (389), and brachial plexitis (33, 41). In the face of acute HIV-1 meningitis or meningoencephalitis, cerebrospinal fluid (CSF) examination usually reveals an increased protein (<100 mg/100 ml), mononuclear pleocytosis (<200 cells per mm³), and normal glucose (165). CSF viral cultures or viral antigen studies may establish the diagnosis before the development of either a systemic or a local antibody response. However, neither the presence of HIV-1 in the CSF by culture or antigen assay (296) nor the demonstration of intrathecal antibody synthesis specific for HIV-1 necessarily indicates the coexistence of clinically symptomatic neurological disease. Viral recovery from the CSF (118) may be as common in the absence of neurological disease as in its presence. Similarly, intrathecal HIV-1-specific immunoglobulin G synthesis during early infection occurs commonly in asymptomatic HIV-1-seropositive individuals (97, 308).

A small percentage of individuals with HIV-1 meningitis will present in subacute fashion and have features of the illness that persist for months. Hollander and Stringari (165) proposed that two forms of meningitis may accompany HIV-1 infection. In a study of 14 patients with relatively preserved immune function, an unexplained CSF lymphocytic pleocytosis was associated with an acute, self-limited meningitis in seven patients and chronic headaches with or without meningeal signs in the other seven patients (165). In four of five CSF specimens studied, HIV-1 was recovered (165). The investigators concluded that, in addition to the acute HIV-1 meningitis associated with recent seroconversion, sporadic episodes of acute and chronic meningitis may complicate HIV-1 infection (165). Even in the absence of any symptoms, abnormal CSF findings are very common in HIV-1-infected individuals (7, 46, 97, 235, 236). Marshall et al. found CSF abnormality in 63% of 424 HIV-1-infected

United States Air Force personnel, 80% of whom were entirely asymptomatic (236). These CSF abnormalities are diverse in nature and include mononuclear pleocytosis, elevated protein, increased immunoglobulin G, and the presence of oligoclonal bands. As with CSF viral recovery, these abnormalities and the demonstration of CSF p24 antigen (296) do not appear to be predictive of the subsequent development of clinically manifested neurological disease (236).

HIV-1 Encephalopathy (HIV-1-Associated Cognitive-Motor Complex)

Shortly after the initial description of AIDS, an unusual, slowly progressive, dementing illness was recognized in association with this disease (34, 342). This disorder was at first referred to as a subacute viral encephalitis, and cytomegalovirus was considered the likely etiology (34, 270, 342). Subsequently, compelling evidence accumulated directly linking HIV-1 to this encephalopathy. This illness has been referred to by several appellations, including AIDS dementia complex, AIDS dementia, AIDS encephalopathy, and HIV-1 encephalopathy. Because of the spectrum of abnormalities observed in association with this disorder, a Working Group of the American Academy of Neurology chose the name HIV-1-associated cognitive-motor complex to include patients with severe manifestations as well as individuals with milder illness (176, 381). The distinction between the mild cognitive deficits associated with HIV-1 infection and clinically evident dementing illness is significant since it is uncertain whether these disorders exist on the same continuum.

The exact incidence of this disorder in HIV-1-infected individuals remains uncertain. Of 144,184 persons with AIDS reported to the Centers for Disease Control between 1 September 1987 and 31 August 1991, 10,553 (7.3%) were reported to have HIV-1 encephalopathy. In 2.8% of the adult patients with AIDS and 5.3% of the pediatric patients with AIDS (176, 179), HIV-1 encephalopathy was the initial manifestation of AIDS. In other studies, the frequency with which HIV-1 encephalopathy was the initial AIDS-defining illness has ranged from 0.8% (26) to 2.2% (216) of adult AIDS patients. In children, it has been reported to be as high as 17.9% (332). Price and colleagues have estimated that at the time of AIDS diagnosis approximately one-third of patients exhibit overt and one-quarter exhibit subclinical AIDS dementia complex (300, 301). These investigators (266) correlated the clinical manifestations of dementia in 70 AIDS patients tracked for 3 years with neuropathological findings obtained at postmortem examination. Forty-one patients with evidence of focal nervous system disease were excluded from analysis, and of the 70 remaining patients, 46 (66%) suffered from a progressive dementia by DSM-III-R criteria. The unexplained cognitive and motor changes were presumed to be attributable to HIV-1 and were characterized as moderate to severe in terms of functional impairment. Indeed, none of the patients were capable of fully independent living.

Deriving the prevalence of HIV-1 encephalopathy from the published literature is difficult because of the prior lack of a standardized definition, differences in the study populations, and disparities in study designs. Extrapolating from their experience, Price and colleagues have estimated that approximately one-third of patients with AIDS-related complex or Kaposi's sarcoma-defined AIDS have unequivocal evidence of HIV-1 encephalopathy and another one-fourth

have subclinical affliction (300). The same investigators have estimated that the preterminal prevalence of overt AIDS dementia complex is approximately 66% and that an additional 25% of preterminal AIDS patients have a subclinical form of the disorder (300). Other studies have suggested a prevalence of HIV-1 encephalopathy of 50% in patients with AIDS (307). The development of effective antiretroviral therapy, such as zidovudine, may have altered the natural history of this disorder and changed the frequency with which it is observed (82, 295). A fivefold decline in the annual incidence was noted in one population following the introduction of zidovudine (295). A phase II placebo-controlled study of zidovudine in patients with AIDS and AIDS-related complex suggests that the annual rate of clinical dementia in patients with Centers for Disease Control stage IV disease is approximately 14% (82). Recent data from the multicenter AIDS cohort study suggest that the incidence of dementia after the development of AIDS is approximately 7% annually, with approximately one-third of patients being demented at the time of death (321).

The incidence of HIV-1 encephalopathy determined at autopsy has varied among different series. In a study of the findings of 345 consecutively performed autopsies of patients dying with AIDS, 68 (19%) had morphological features of HIV-1 encephalopathy (198). In a large series incorporating seven separate neuropathological studies (206) that comprised 926 patients, the estimates for HIV-1 encephalopathy ranged from 13.3 to 62.9%, with a composite total of 30.9%. Navia and colleagues have suggested that as many as two-thirds of autopsied AIDS patients have this encephalopathy (265), whereas other investigators have found a higher incidence, between 70 and 93% (84, 145, 148, 184, 197, 270). A study from San Diego, Calif., of 107 brains from autopsies of patients with AIDS, which were collected during a 3-year period, revealed that while only 16% had the characteristic hallmarks of HIV-1 encephalitis, more than 50% had evidence of HIV-1 infection (238).

Overt HIV-1 Encephalopathy

Clinically, HIV-1 encephalopathy is characterized by an insidious onset of a disturbance in intellect. Fatigue and malaise, headaches, increasing social isolation, and loss of sexual drive are noted. Rarely, the disorder may begin abruptly and progress rapidly. Patients often complain of increasing forgetfulness, difficulty concentrating and reading, and a slowness in their thinking. Job performance declines, and eventually self-care may become problematic. A diagnosis of depression is frequently considered. However, dysphoria is typically absent (301). Language skills suffer and word finding difficulties are common. Some patients complain of incoordination, imbalance, gait disturbances, or tremor. Painful peripheral dyesthesias may occur and are typically the result of a superimposed HIV-1-related peripheral neuropathy.

Sleep disturbances are reported, with polysomnographic studies indicating a distortion of sleep architecture (271, 272), and both focal and generalized seizures have been described (19, 168, 283). In fact, in a large percentage of HIV-1-infected persons with seizures, no etiology other than HIV-1 could be identified for the seizures (19, 168).

HIV-1 encephalopathy typically occurs in the context of advanced immunosuppression and coexistent systemic disease (136, 139, 300, 301, 333, 339, 364) but may be the presenting or even sole manifestation of HIV-1 infection even before the infected individual exhibits any other ill-

nesses characteristic of impaired immunity (22, 52, 267). Approximately 3% of adults with AIDS present with dementia (177, 242, 267).

The typical patient with overt HIV-1 encephalopathy appears debilitated and chronically ill as a consequence of advanced immunosuppression. Physical examination often reveals the hallmarks of full-blown AIDS with temporal and general body wasting, alopecia, seborrheic dermatitis, and generalized lymphadenopathy. Bedside mental status examination in advanced HIV-1 encephalopathy reveals a slowing of mental processing (bradyphrenia). Eye movement abnormalities are common. These ocular motility disorders include slowed saccadic eye movements (252, 268, 315), hypometric saccades (76), overshoot dysmetria (114), fixational instability (76), and defective smooth pursuits (76). Currie and colleagues found these eye movement abnormalities useful predictive markers for the development of HIV-1 encephalopathy (76). There is a diminution of facial expression (facial hypomimia). The voice is hypophonic and monotonous, and speech production is typically slow. Stuttering has also been reported (107). Coordination is impaired, consistent with involvement of the basal ganglia (8). This impairment may be observed even in early stages of the illness (8). Fine movements are performed slowly and awkwardly. Such tasks as buttoning shirts, writing, cutting food, and shaving may prove difficult (313). A fine, irregular tremor that is most evident during sustained postures of the upper limbs is frequently detected. A resting tremor is not observed though features reminiscent of Parkinsonism, namely, bradykinesia, postural instability, cogwheel rigidity, hypomimetic facies, and eye movement disorders, may be observed. The motor tone is increased. The gait is slow and clumsy with diminished arm swing and postural instability. In early stages of HIV-1 encephalopathy, brisk walking, pivoting, and walking heel-to-toe may betray abnormalities (313). Parkinsonian features may be intensified by the administration of dopamine receptor blockers, including prochlorperazine and metoclopropamide (93, 164, 170), and the patient may literally be "frozen" in bed as a consequence. Dystonia has been reported in the absence of neuroleptic exposure (253). Muscle stretch reflexes may be increased. However, the frequent superimposition of peripheral neuropathy may result in a loss or diminution of ankle jerks as well as diminished sensory perception in distal extremities. Evidence of corticospinal tract involvement may also include Hoffman's and Babinski's signs and crossed adductor reflexes. Frontal release signs, including snout, suck, involuntary grasps, and palmomentals, nuchocephalic and glabellar, are typically elicitable. A generalized motor weakness is not uncommon. The presence of weakness confined to the lower extremities, particularly when associated with incontinence, brisk lower extremity reflexes, Babinski's signs, and lower extremity sensory loss, should suggest the possibility of an underlying myelopathy. In advanced stages of the illness, the patient is bed bound and incontinent.

HIV-1 Encephalopathy in Children

Children infected with HIV-1 may also develop an encephalopathy that can be either progressive or static (24, 103). As in adults, the neurologic manifestations may occur before any signs of immunodeficiency, exemplified by the infant described by Davis and coworkers who developed progressive spastic diplegia and dementia at the age of 6 months resulting from HIV-1 infection in the absence of any evi-

dence of immunosuppression (81). However, generally, the neurologic disease progresses in tandem with the degree of immunodeficiency (104). In one study of 36 infected children, the incubation period from initial perinatal infection to the development of encephalopathy varied from 2 months to 5 years (104). The encephalopathy is characterized by a developmental delay or the loss of motor milestones and intellectual abilities that had been acquired previously (104, 274). Examination may reveal weakness with pyramidal tract signs, extrapyramidal signs, pseudobulbar palsy, ataxia, and secondary microcephaly. Myoclonus and seizures are observed.

Psychiatric Disorders

A wide variety of psychiatric disorders may be seen with HIV-1 encephalopathy (75, 108, 187, 226, 273, 358). These psychiatric manifestations may be seen in isolation. Delirium characterized by a clouding of consciousness with reduced capacity to shift, focus, and sustain attention to stimuli and accompanied by excessive psychomotor activity and hallucinations and delusions is sometimes observed. In one study, delirium was the most frequent diagnosis in patients with AIDS for whom a psychiatric consultation had been requested. Risk factors for its development include drug and alcohol use as well as prior brain damage (276). Psychoses may also attend HIV-1 encephalopathy (226) and, in rare instances, be the presenting manifestation of the disorder (22, 75). In perhaps 10 to 15% of the affected individuals, the illness may present as a frank psychosis. A triad of mood disturbance, thought disorder with grandiose delusions, and severe memory deficits has also been described (190). Similarly, organic affective disorders, mania and depression, may also accompany HIV-1 encephalopathy (226). Severe depression may be a consequence of organic disease and be poorly, if at all, responsive to antidepressant therapy (40). Anecdotal reports suggest that treatment with zidovudine results in improvement in depressive symptomatology that had been unresponsive to prior antidepressant activity (288). The possibility of a drug-induced psychiatric disorder should not be readily discounted. Mania in association with zidovudine (382) and aggressive psychosis with corticosteroid administration (42) have been reported in patients with AIDS. Exquisite sensitivity to anticholinergic drugs with resultant confusion (289, 304) and to dopamine receptor blockers, such as metoclopropamide and a variety of widely used neuroleptics, with resultant severe Parkinsonism (164), is not uncommonly observed. The development of either of the above in a young, HIV-1-infected patient should suggest the presence of an otherwise unsuspected HIV-1 encephalopathy.

Neuropathology

The gross pathology of HIV-1 encephalopathy is characterized by brain atrophy with sulcal widening and ventricular dilatation. Meningeal fibrosis may occasionally be observed. Histologically, the most common and distinctive feature of this illness is white matter pallor (265). This pallor largely appears to be the result of perivascular demyelination. It is chiefly located in the periventricular and central white matter and is accompanied by an astrocytic reaction. In brains with mild myelin damage, there is an increase in the numbers of oligodendrocytes, a reactive hyperplasia that has been interpreted as an attempt to repair myelin damage (105). A significant decline in the number of oligodendro-

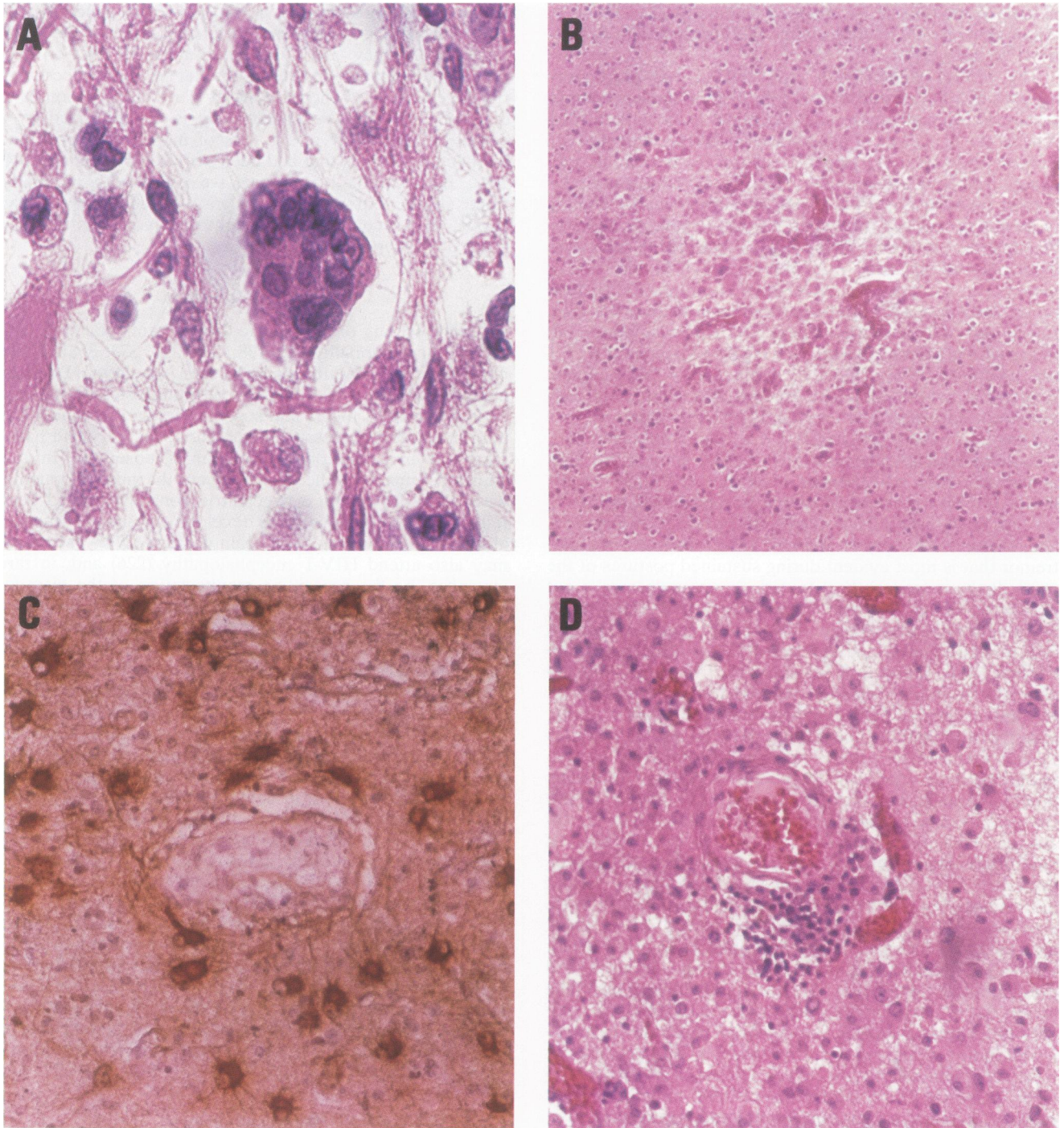


FIG. 2. Neuropathologic characteristics of HIV-1 encephalitis. (A) Multinucleated giant cell. (B) Macrophage/microglial cell nodule. (C) Perivascular astrocytosis. (D) Perivascular mononuclear infiltration of subcortical white matter. Panels A, B, and D were stained with hematoxylin and eosin. Panel C was stained with a polyclonal antibody to the astrocyte-specific antigen glial fibrillary acidic protein by an immunoperoxidase method and counterstained with hematoxylin.

cytes is observed with advanced disease and severe myelin damage (145). Rarefaction of the white matter and, in severe cases, diffuse or focal microvacuolation may be detected. In the series of Kato et al., true demyelination appeared to be rare, occurring in only 1 of 53 brains from patients with AIDS (184). Multinucleated giant cells (Fig. 2A) are believed

by some investigators to be a pathologic hallmark of the disease, but others observe this only rarely (5, 6). The multinucleated giant cells appear to result from direct virus-induced cell fusion (301). This phenomenon appears to be identical to one that occurs *in vitro* in HIV-1-infected cell cultures (294). These multinucleated giant cells appear to

cluster around the microvasculature but are also present in normal neuropils, gliomesenchymal cell nodules, and cavitating lesions (310). Other microscopic features include microglial nodules (Fig. 2B), diffuse astrocytosis (Fig. 2C), and perivascular mononuclear inflammation (Fig. 2D). While some investigators have correlated the presence of microglial nodules with the presence of cytomegalovirus infection (184), others have not (279). In a study of 53 brains from AIDS patients, Kato and colleagues detected microglial nodules in 45% of the brains, and of these, 46% were accompanied by cytomegalovirus infection (184). Ciardi and colleagues, employing immunohistochemical techniques as well as routine histological studies, have demonstrated increased numbers of glial fibrillary acidic protein-expressing astrocytes and microglial cells in the brains of HIV-1-infected individuals, particularly in the subpial regions (55). These investigators noted a correlation between the severity of the encephalopathy in the white matter and the increased number of glial fibrillary acidic protein-expressing cells (55). Mononuclear inflammation observed with HIV-1 encephalopathy may be particularly prominent in the brainstem (310). Ependymal lesions are also observed frequently in the brains of adults and infants with HIV-1 encephalopathy (310).

Rarely, other pathology has been associated with HIV-1 encephalopathy, including spongiform encephalopathy (11, 190, 331). Artigas and colleagues contend that this type of encephalopathy found in different areas of the brain, including microcystic cavitations of the gray matter with associated neuronal loss, is a frequent finding in AIDS dementia (11). Increasing interest has focused on cortical changes occurring as a consequence of HIV-1 infection. Early studies (36, 84) described cortical abnormalities in the brains of adults with AIDS, and nerve cell loss was detected in affected children (333). Using quantitative techniques, Wiley and colleagues have demonstrated significant thinning of the neocortex in patients with HIV-1 encephalopathy (376). In addition to the loss of neurons, these investigators showed a loss of synaptic density and vacuolation of dendritic processes (238, 376). The dendritic and synaptic damage has been correlated with the presence of HIV-1 in the neocortex (239). In other studies, quantitative assessments of neurons in the frontal cortex have revealed a significant decrease in their numbers in HIV-1-infected brains compared with control brains (106). Isolated cases of prominent cortical atrophy with neuronal loss (145) and massive neuronal destruction accompanied by diffuse necrotization (135) have been reported. Not unexpectedly, in light of the clinical features of HIV-1 encephalopathy, the basal ganglia and related deep nuclear structures exhibit abnormalities in HIV-1 infection. Subclinical degeneration of the substantia nigra was detected by estimates of the volume density of melanin and quantitative assessments of pigmented and nonpigmented neuronal cell bodies in the pars compacta of the substantia nigra (309). This observation may explain the sensitivity of patients with AIDS to drug-induced Parkinsonism (309).

While there is a correlation between the clinical and pathological features of HIV-1 encephalopathy (314), the relationship between them remains uncertain. In clinically severe HIV-1 encephalopathy, the brain may show few changes on histopathological study, whereas nondemented patients may have remarkable pathological changes characteristic of HIV-1 encephalopathy (377). The diagnosis of HIV-1 encephalitis is made by observing multiple disseminated foci of microglia, macrophages, and multinucleated giant cells. The morphological definition of HIV-1 leukoen-

cephalopathy includes diffuse damage to white matter with myelin loss, reactive astrogliosis, and the presence of macrophages and multinucleated giant cells. For both of these syndromes, the presence of multinucleated giant cells is a prerequisite for diagnosis. In their absence, the presence of HIV-1 antigen or nucleic acids as determined by immunocytochemistry or in situ hybridization is required (37). Generally, a broad spectrum of neuropathological findings that include features of these pathological syndromes exist. In children, the pathologic features of HIV-1 encephalopathy occur as a unique constellation characterized by diminished brain weight, inflammatory cell infiltrates, multinucleated giant cells, vascular calcifications, perivascular inflammation, and white matter changes (334). At autopsy, the brains of children with HIV-1 infection weigh less than those of normal controls (202). Although multinucleated giant cells, microglial nodules, and white matter pallor are commonly observed in the brains of children and adults, the most frequent finding in children is vascular or juxtavascular basophilic mineralization located in either the basal ganglia (putamen and globus pallidus, but not caudate) or the frontal lobe white matter (333). This mineralization of the basal ganglia is detectable on radiographic imaging and appears to be unique to childhood HIV-1 encephalopathy (23, 334). Inflammation of parenchymal blood vessel walls (cerebral vasculitis) has been observed in approximately 30% of the brains of children with HIV-1 infection (333). As in adults, the genome of HIV-1 can be demonstrated in the brains of these patients by in situ hybridization techniques (305, 334).

Just as the frequency of clinically detected AIDS dementia is changing (295), the frequency and pattern of neuropathology are changing (310). In 300 consecutive autopsies of patients with AIDS, Rhodes and Ward noted a continuing linear decrease in the presence of gliomesenchymal cell nodules and chronic perivascularitis (310). They attributed these decreases to the use of antiretroviral therapy, in particular, zidovudine (310). However, during the 3-year course of their series, they noted an increase in the incidence of perivascular macrophages and multinucleated giant cells (310).

NEUROTROPISM OF HIV-1

Evidence for Direct Infection of the CNS by HIV-1

Direct infection of the nervous system by HIV-1 was not appreciated in the early years of the AIDS epidemic. Neurological complications associated with AIDS were largely attributed to opportunistic infections and depression. In 1985, by sequence similarity and morphological criteria, HIV-1 was classified as a lentivirus (140, 306, 320, 344). In that same year, HIV-1 DNA and RNA were detected by Southern blot and in situ hybridization in 5 of 15 brains from patients with AIDS (337). Also in that year, Epstein and colleagues detected retrovirus-like particles in the brains of three patients with AIDS by using electron microscopy (102). These particles were localized to multinucleated giant cells and occasionally to astrocytes (102). Several groups reported the direct isolation of HIV-1 from CSF and brain tissue from patients presenting with neurological symptoms (161, 215). In addition, Ho and colleagues isolated virus from the spinal cord of a patient with myelopathy and from the sural nerve of another patient with peripheral neuropathy (161). These results led to the reevaluation of HIV-1 as a

neurotropic virus and encouraged many groups to investigate the cell types in the nervous system that were infected with HIV-1.

A variety of techniques have been used to localize HIV-1 in CNS tissue, including in situ hybridization with biotinylated and radiolabelled probes, electron microscopy, and immunocytochemistry. Using all three of these techniques, Koenig and colleagues demonstrated HIV-1 in mononucleated and multinucleated macrophages within the CNS (199). Gabuzda and colleagues examined frozen sections from 13 patients by immunocytochemistry for viral antigen and found HIV-1 associated with capillaries in the cortex of temporal, frontal, and parietal lobes in 5 of the 13 samples (116). They noted that the positive staining was often located near microglial nodules and that the stained cells morphologically resembled monocyte/macrophages (116). Wiley and colleagues, using in situ hybridization, immunocytochemistry, and electron microscopy, localized HIV-1 to capillary endothelial cells, mononuclear inflammatory cells, and multinucleated giant cells in 12 patients with AIDS and evidence of viral encephalitis (377). In 1 of the 12 patients with severe CNS infection, virus was also seen in astrocytes and neurons (377). In a postmortem study of three AIDS patients with extensive encephalitis, Michaels and colleagues found HIV-1 localized primarily to monocyte/macrophages, microglial cells, and multinucleated cells (254). In a large study of 102 brains from patients with AIDS and subacute encephalopathy, Kure and colleagues found HIV-1 antigen in mononucleated and multinucleated cells in 90% of adult and 50% of pediatric specimens (206). In double-labelling experiments, the positive cells were found to belong to the monocyte/macrophage/microglial cell population. No colocalization of viral antigen with astrocytes, neurons, or lymphocytes was observed. HIV-1-infected macrophages have also been detected in spinal cords of AIDS patients presenting with vacuolar myelopathy (85, 314). In one study, Peudener and colleagues antigenically and functionally distinguished microglial cells from monocyte/macrophages by several criteria (290). In their study, HIV-1 localized to cells in the CNS that bore monocyte/macrophage markers but not to cells expressing microglial cell markers (290). Recently, Tornatore and colleagues detected HIV-1-infected astrocytes in 4 of 12 brain specimens from pediatric AIDS cases with well-documented HIV-1-associated dementia (reviewed in reference 100). In this study, infected astrocytes were detected by immunocytochemistry and viral nucleic acid was colocalized in glial fibrillary acidic protein-positive cells, using in situ hybridization, with a radiolabelled HIV-1 probe. The infected astrocytes were seen in subcortical white matter in areas that contained large numbers of infiltrating HIV-1-positive mononuclear cells. Both the infected astrocytes and infiltrating monocytes were seen only in sections with moderate to extensive HIV-1-associated leukoencephalitis. The authors suggest that, in areas where the HIV-1 viral burden may be high because of infiltration of infected mononuclear cells, astrocytes can become infected or mononuclear cells elaborate cytokines that activate latently infected astrocytes to express virus. Similar results were obtained independently by Epstein and Gendelman (100).

It is clear that more sensitive techniques, such as in situ polymerase chain reaction, are needed to determine whether other types of cells in the CNS harbor HIV-1 at levels below those detectable by currently available assays (16–18).

T-Cell-Versus Macrophage-Tropic Strains

The selective depletion of CD4⁺ T lymphocytes in AIDS patients together with the finding that HIV-1 could productively infect this population of cells in vitro clearly established CD4⁺ T cells as a primary site of HIV-1 replication (20, 121, 195, 245, 294). The subsequent demonstration that CD4 functioned as the cell surface receptor for HIV-1 explained the tropism of the virus for these cells (78, 194, 244–246). The rate of viral multiplication and concomitant cell death in these cultures was correlated with the state of activation of the T cells (245). T cells isolated from patients and cultured in the presence of phytohemagglutinin and IL-2 were quickly killed by the virus. Long-term cultures of HIV-1-infected T cells were possible when the cells were grown under conditions that would not maintain the state of activation of the cells. In one report, a long-term noncytotoxic persistent infection of normal T cells by HIV-1 was observed (169). In addition, virus isolates that grew well in primary culture of T cells did not always grow well in CD4⁺ T-cell lines. However, viral variants that grew efficiently in the cell lines could be selected for by continuous passage of the virus in these cells. Cheng-Mayer and colleagues demonstrated that several different HIV-1 primary isolates and a molecularly cloned isolate passaged in different cell types displayed altered growth rates and tropisms for different cells (50). Changes in the molecular weight of gp120 were correlated with these changes (50).

Similar to what had been shown for other members of the lentiviral subfamily (130–132, 264), HIV-1 was also shown to infect cells of the monocyte/macrophage lineage (126, 127, 129, 233, 248, 292, 293). Virus binding and infectivity of these cells also depended on expression of the CD4 receptor (63, 221, 232, 233). In many instances, the replication of HIV-1 in macrophages and in macrophage-derived cell line cultures was very inefficient compared with the growth of the virus in primary T cells and T-cell lines. This restricted activity was not dependent on levels of CD4 as many of the macrophage cell lines expressed higher levels of CD4 than their T-cell counterparts. In fact, different isolates of HIV-1, often from the same patient, varied in their tropisms for different cell types (4, 12, 50, 51, 54, 147, 150, 191, 371). In general, HIV-1 isolated from AIDS patients early in disease replicated less efficiently and had a narrower host range in cell culture than HIV-1 isolated from the same patients at later stages of the disease (12, 54, 110). Often, strains of HIV-1 that infected T cells efficiently grew less well or not at all in macrophage cultures and strains that grew well in macrophage cultures were less efficient in T-cell cultures. This observation led to the identification of T-cell and macrophage-tropic variants of HIV-1. A summary of these different strains, their primary sites of isolation and passage histories, and the cells that they infect is given in Table 2.

Viral and Cellular Determinants of Tropism

Investigation into the viral determinants of T-cell tropism showed that the binding of virus to the CD4 molecule was mediated by gp120, the product of the *env* gene of HIV-1 (388). The *env* gene of HIV-1 encodes a 160-kDa precursor protein that is cleaved by a viral protease into a surface unit monomer of 120 kDa (gp120) and a transmembrane 41-kDa species (gp41). Antibody mapping studies and site-directed mutagenesis have precisely defined the regions on both the gp120 and CD4 molecules that are necessary for binding of virus to CD4⁺ cells (9, 66, 208). The increased efficiency of

TABLE 2. Some commonly used virus strains and their properties^a

Virus strain	Source	Host range	Reference(s)
HIV-1 _{Ada-M}	Peripheral blood of an AIDS patient, isolated on cultures of blood-derived monocyte/macrophages	Human monocytes, lymphoblasts, and colonic epithelial cells	133
HIV-1 _{Ba-L}	Primary culture of monocyte/macrophages from human infant lung	Peripheral monocytes and macrophages and CD4 ⁺ T lymphocytes	127
HIV-1 _{BRVA}	Autopsied brain of AIDS patient with progressive dementia, propagated in peripheral blood monocytes	Human PBMC, ROHA and U937 monocytoid cell lines	4, 257
HIV-1 _{JR-CSF}	Filtered CSF of AIDS patient JR, cultured in PBL	Human PBMC and monocytes, a low-level persistent infection in primary human brain gliomas	43, 201
HIV-1 _{JR-FL}	Frontal lobe tissue of AIDS patient JR, propagated in PBL	Human PBL and monocytes	201
HIV-1 _{NL4-3}	Chimeric strain composed of NY5 and LAV, passaged in A3.01 human T-cell line	Several T-cell lines as well as several non-T-cell lines, infects cells from a wide variety of species, produces a low-level persistent infection in cultures of human fetal brain astrocytes	2
HIV-1 _{SF2}	PBMC of an AIDS patient, cultured in PBMC from seronegative donors	Human PBMC, T-cell lines, monocyte cell lines	214
HIV-1 _{SF162}	CSF of AIDS patient, propagated in PBMC	Human PBMC and primary macrophages	49
HTLV-III _B /H9	Pooled PBL and bone marrow from several AIDS patients, cultured in the H9 human T-cell line	Human CD4 ⁺ T-cell lines and PBL	294, 306
HTLV-III _{CC} /H9	Peripheral blood of an AIDS patient, cultured in H9 human T-cell line	CD4 ⁺ T-cell lines and PBL	122
HTLV-III _{MN} /H9	Peripheral blood of an AIDS patient, cultured in H9 human T-cell line	CD4 ⁺ T-cell lines and PBL	121
HTLV-III _{RF} /H9	Peripheral blood of an AIDS patient, cultured in H9 human T-cell line	CD4 ⁺ T-cell lines and PBL	294
LAV.04/A3.01	Peripheral blood of an AIDS patient, cultured in A3.01 human T-cell line	CD4 ⁺ T-cell lines and PBMC	20

^a Abbreviations: NY5, New York-5; LAV, lymphadenopathy virus; HTLV, human T-cell leukemia virus.

virus multiplication in activated versus nonactivated T cells was not correlated to binding of virus to CD4 (245). Robinson and colleagues, using a molecularly cloned isolate of HIV-1, demonstrated that the rate and efficiency of virus uptake into four different T-cell lines correlated with the degree of permissiveness of each cell line to viral infection (346). Cann and colleagues also demonstrated that transfection of nonpermissive cells with HIV-1 DNA results in transient virus production in those cells (43).

Detailed analysis of T-cell and macrophage-tropic variants of HIV-1 identified additional regions outside of the CD4-binding site of gp120 as important determinants of viral tropism (172, 174, 221, 275). Specifically, changes in the V3 loop region of the gp120 molecule were implicated (172, 174). It has been proposed that the V3 loop serves as a substrate for a cell surface protease whose action aids in the fusion of the viral envelope to cells. Therefore, changes in this region could affect tropism by altering the recognition site on the V3 loop for this protease (57, 128). In support of this idea is the demonstration by Robinson and colleagues that the efficiency of viral fusion and entry into cells is an important

factor in determining tropism (346). A third important region of the virus in determining tropism resides in a 41-kDa transmembrane protein associated with gp120. Changes in this region have also been found to alter the host range of HIV-1 (115).

Tropism of Virus Isolates Obtained from Neural Tissue

Several laboratories have reported the direct isolation and characterization of HIV-1 from the CNS (4, 50, 54, 201). Similar to what had been observed of viruses isolated from peripheral blood, the CNS-derived isolates were found to differ in their tropism for different cell types. In one study, an isolate derived from CSF (JR-CSF) grew well in peripheral blood lymphocytes (PBL) but did not grow efficiently in primary macrophage cultures (201). Another isolate derived from the frontal lobe of the same patient (JR-FL) grew well in both PBL and macrophage cultures (201). Interestingly, only the CSF-derived isolate was able to infect explants of a brain glioma. The infection in the glioma explant culture was characterized as a low-level persistent infection (201). In

another study, an isolate obtained from brain biopsy (HIV-1br) replicated in both T-cell and monocyte cell lines (4). This isolate was found to have duplicated a portion of the *nef* gene (4). The astrocyte cell line MG138 has been shown to be susceptible to infection with virus isolated from either the CSF or blood (191). In a larger study comparing paired isolates from the blood, peripheral blood mononuclear cells (PBMC), and CNS (CSF) of six individuals, the blood-derived isolates replicated more efficiently in T-cell and glioma cell lines, whereas the CSF isolates replicated better in primary macrophage cultures (51). One of the CNS isolates taken from brain tissue at autopsy had characteristics similar to those of the blood-derived isolates. The brain tissue from which this isolate was derived had been contaminated with blood (51). In a similar study, Fenyo and colleagues were able to distinguish virus isolated from the CSF and PBMC on the basis of their replicative capacity, cytopathic effects, and protein profiles in different T-cell and monocytoid cell lines (110). Several groups have also reported that virus isolated from CSF and blood can be distinguished genotypically by differences in restriction enzyme digest patterns (150, 201). This has led to the suggestion that variants of HIV-1 can coexist in different tissues of a single individual. The recent finding in experiments with transgenic mice that an LTR derived from a brain isolate was expressed in the brain of the mice but a construct containing the LTR from a blood isolate could not be expressed supports this conclusion (65).

Growth of HIV-1 in Cells Derived from Neural Tissue

In vivo, HIV-1 infection has been demonstrated in monocyte/macrophages, microglial cells, and, in cases of moderate to severe encephalitis, astrocytes. Of these, only the microglial cell and the astrocyte are resident components of the CNS. Unlike astrocytes, microglial cells are bone marrow-derived cells that migrate to the CNS early in the course of development (160). Watkins and colleagues have shown that microglial cells are infectible with HIV-1 in vitro (370). The microglial cells were isolated from a temporal lobe resection from a patient with epilepsy. Only macrophage-tropic strains of HIV-1 were capable of infecting these cells in culture. Two T-cell-tropic strains of HIV-1 and two strains of HIV-2 failed to infect the cells. Astrocytes that were present in the culture did not express HIV-1 Gag protein and were deemed not to be infected with any of the strains tested. The infected microglial cells formed clusters of multinucleated cells that resembled the multinucleated giant cells that some consider hallmarks of HIV-1 infection in the CNS. In a subsequent report, Jordan and colleagues demonstrated that infection of microglial cells is CD4 dependent (181). The tropism of HIV-1 for microglial cells was also found to be controlled by regions of the Env protein that also control macrophage tropism (335, 370).

In contrast to these reports, Peudenier and colleagues have found that microglial cells are not infectable with HIV-1 (290). In their study, brain microglial cells were distinguished from monocyte/macrophages on the basis of their expression of Fc, CD68/Ki-M7, and CD11B/CR3 receptors and the lack of CD4, CD14, and CD68/KiM6. Monocyte/macrophage cells expressed all of these markers, and both microglial cells and monocyte/macrophages were capable of phagocytosing zymosan particles. In this study, HIV-1 localized to cells in the CNS deemed to be monocyte/macrophages and not to microglial cells. Furthermore, only cells

that bore macrophage/monocyte markers were infectable with HIV-1 in vitro (290).

Several laboratories have reported the infection of brain-derived cells in vitro. Primary human fetal dorsal root ganglion-derived glial cells, glioma explants and cell lines, neuronal cell lines, and primary human fetal glial cells have all successfully been infected with different strains of HIV-1 (44, 53, 88, 152, 191, 194, 205, 217, 318, 361, 371) (Table 3). The infectivity of these brain-derived cells is very low compared with the infectivity of lymphoid cells and microglial cells. Often detection of infectious progeny virus comes only after cocultivation of the brain-derived cells with highly permissive lymphoid cells. In one study, cultures of human fetal astrocytes were successfully infected with HIV-1 by coculturing the cells with a T-cell line that was infected with HIV-1 (361). These cells could also be infected with cell-free virus. The infection was characterized by an initial burst of viral p24 production that declined over time. Viral p24 could be detected several weeks later when the cultures were cocultured with uninfected T cells (361). It was shown that cell-to-cell contact was not necessary for the reappearance of infectious virus because a similar effect was seen when the cells were separated by a semipermeable membrane. The cytokines TNF- α and IL-1 β were found to mimic the effect of coculturing the glial cells with the T cells (13, 361). The authors suggested that glial cells could be an unidentified reservoir of HIV-1 in the CNS and that infiltrating lymphoid cells or macrophages could reactivate latent HIV-1 in these cells.

The cellular receptor for HIV-1 on lymphoid cells and microglial cells, CD4, has not consistently been demonstrated on cells of neuronal origin. In addition, antibodies to CD4 and soluble forms of CD4 that block the infectivity of HIV-1 in lymphoid cells do not block infection of neuronal cells (56, 205, 371, 375). The lack of the CD4 receptor on neural cells cannot wholly account for the slow growth of HIV-1 in these cell types as transfection of the cells with viral DNA does not result in improved viral replication. In addition, Harouse and colleagues recently demonstrated that the replication kinetics of HIV-1 in glial cells constitutively expressing CD4 did not differ from their non-CD4-expressing counterparts (154). They also showed that the efficiency of virus entry into these cells was the same whether or not the cells expressed CD4 (154). Several groups have shown recently that galactocerebrosides may serve as receptors for HIV-1 on CD4-negative cells, including astrocytes and colon epithelial cells (28, 152, 384). In these studies, antibodies to galactocerebrosides inhibited the entry of HIV-1 into cells, and in one study, recombinant gp120 specifically interacted with galactocerebroside (28).

MECHANISMS OF HIV-1 DAMAGE TO THE CNS

The fact that HIV-1 causes damage in the CNS has been documented in numerous reports of the clinical consequences of finding HIV-1 virions in brain (199) and spinal cord (85, 161, 314). Unlike other virus infections in the CNS, the mechanisms of HIV-1 damage have eluded investigations since there is little evidence that HIV-1 directly infects neural cells. This observation has prompted the suggestion that virus damage either occurs because of direct infection of a relatively small population of cells that may be difficult to detect or is caused by indirect effects following release of neurotoxic factors from infected non-neural cells such as macrophages.

TABLE 3. Susceptibility of brain-derived cells and cell lines to infection with various strains of HIV-1

Cells	Virus strain used	Type of infection	Demonstrated by:	Reference(s)
Primary cells				
Human fetal DRG glial cells (GFAP ⁺)	HTLV-III _B ^a	Low-level noncytopathic; not blocked by anti-CD4	p17, p24	205, 375
Human fetal glial (GFAP ⁺)	HTLV-III _B	Low-level noncytopathic	RT ^b activity, viral particles by EM, ^c p17, p24	225
Human fetal glial (GFAP ⁺)	HIV-1 _{NL4-3}	Low-level persistent infection reactivated by cytokines, noncytopathic	RT, p17, p24, recovery of infectious virus on CD4 ⁺ cells	361
Adult human microglial cells	HIV-1 _{AD87(M)} , HIV-1 _{BaL}	Cytopathic, blocked by anti-CD4, formation of multinucleated cells, not infected by two T-cell strains or HIV-2, GFAP ⁺ cells in culture not infected	p24, p17, RT, EM	181, 335, 370
Cell lines				
U251MG (GFAP ⁺)	HIV-1	Low-level noncytopathic	p55, p24, in situ hybridization for viral RNA	88
U138MG (GFAP ⁺), U251MG (GFAP ⁺)	HTLV-III _B	Low-level noncytopathic	RT, p24, rescue of infectious virus on CD4 ⁺ cells	371
U138MG (GFAP ⁺)	HTLV-III _B	Low-level noncytopathic	Rescue of infectious virus on CD4 ⁺ cells	53
SK-N-MC (neuroblastoma)	HTLV-III _{RF}	Low-level persistent, noncytopathic, not blocked by anti-CD4	p24, rescue of infectious virus on CD4 ⁺ cells	217
SK-N-MC, U373-MG	HTLV-III _B	Low-level persistent, noncytopathic, not blocked by anti-CD4, blocked by antibodies to galactoceramides	p24, rescue of infectious virus on CD4 ⁺ cells	112,152, 153

^a HTLV, human T-cell leukemia virus.

^b RT, reverse transcriptase.

^c EM, electron microscopy.

Direct Infection of Neural Cells

There is no evidence that HIV-1 is found in neurons, although neuronal loss is characteristic of many cases of HIV-1-associated encephalopathies. For example, Everall and colleagues (106) determined by morphometric assay that brain tissue from AIDS patients had a 38% loss of neurons compared with a control group. Others have reported loss of large neurons in the neocortex (376), axonal loss in the optic nerve (357), and particularly interneuron loss in the hippocampus (239). Human fetal or adult neurons in culture derived from either the CNS or the peripheral nervous system also do not appear susceptible to HIV-1 infection (205, 361). Recently, however, the HIV-1 LTR from isolates from either frontal lobe or CSF, JR-FL or JR-CSF, respectively, was expressed in the brains of transgenic mice, particularly in neurons (65). The HIV-1 LTR of a lymphotropic strain was not expressed in CNS tissues in this study, which correlates with other reports (212, 341, 367). Examination of glial cells in brain tissue from AIDS patients has shown some evidence of HIV-1 infection. A few astrocytes that contained HIV-1 Gag proteins were identified in adult brains (47, 102, 377). The myelin sheaths that surround neurons in the CNS have been shown to be severely damaged in AIDS brain tissue (265). However, there is no evidence of direct infection of the myelin-producing oligodendrocytes in the CNS by HIV-1 (265). Reports of HIV-1

infection of astrocytes in pediatric AIDS patients with encephalopathy have suggested that HIV-1 can establish a latent infection in these cells (100). Generally, HIV-1 infection in brain is not abundant and does not seem to correlate with clinical severity of disease or histopathology. The extent of direct infection with HIV-1 in neurons and glial cells may not be defined until more sensitive techniques such as in situ amplification of the HIV-1 genome by polymerase chain reaction analysis and subsequent identification of virus-amplified viral genes are used, as has been done with HIV-1-infected peripheral lymphocytes (16-18).

Effects of Nonstructural HIV-1 Proteins

Several of the HIV-1 regulatory proteins have been implicated in causing damage to neuronal cells. The primary amino acid sequence of Nef shares homology and structural similarity with a scorpion toxin that can interact with neuronal K⁺ channels, resulting in a reversible increase in ion flux (374). The scorpion peptide itself is homologous to the V3 neutralizing domain of the viral gp120 envelope protein and demonstrates relatedness with structural proteins (VP2) of neurotoxic picornaviruses and the G-membrane protein of rabies virus (125). Partial sequence homology of the transmembrane envelope viral protein, gp41, shows similarities to scorpion peptide, particularly in its ability to interact with cellular surface molecules involved in ion-gated channels. In

a glial cell model of infection, the Nef protein can be synthesized in different antigenic forms, and it has been suggested that this might play a role in the establishment of viral latency in these cells (200).

The major HIV-1 regulatory protein, Tat, has a clear function in transactivation of early genes for viral transcription as well as effects on host cell transcription (70). There is one report that Tat is able to induce cytopathic effects in cultured rodent glioma and neuroblastoma cells and to affect rat brain synaptosomal membranes (224, 319). Binding of Tat affects membrane permeability, causing depolarization and altering membrane resistance. Since Tat is secreted from infected cells and can diffuse into neighboring cells (113), it is possible that it can alter cellular functions in cells in which it is not synthesized.

Effects of Structural HIV-1 Proteins

Experiments involving HIV-1 binding and its consequences have been emphasized in attempts to understand mechanisms of neuronal injury in HIV-1 infection. The envelope proteins have received significant attention in these experiments, particularly the gp120 outer surface molecule that interacts with the cellular CD4 receptor. In one of the first series of experiments, similarities of gp120 and neuroleukin were identified by competition for similar cell surface receptors. In these studies, gp120 could inhibit the growth-promoting properties of neuroleukin for chick dorsal root ganglion sensory neurons (210). The viral gp120 was also shown to be toxic to mouse hippocampal neurons in culture (29). Vasoactive intestinal peptide, which has sequence similarity to the CD4-binding domain of the gp120 molecule, blocked the toxic effects of gp120 on these cells (29). The toxicity of gp120 for these cells was most pronounced when astrocytes were also present in the culture, suggesting that the toxicity could be related to some other factor released from infected cells (29).

Some of the strongest evidence for neurotoxicity of the gp120 molecule comes from experiments in which rodent hippocampal neurons or retinal ganglion cells show cell loss due to increases in intracellular Ca^{2+} (89). Only the glycosylated form of gp120, whether derived from a neurotropic or a lymphotropic strain, was toxic in these assays. Calcium channel antagonists such as nimodipine and nifedipine block this effect (89). This type of neuronal injury may be similar to that of excitatory amino acids of the glutamate type on *N*-methyl-D-aspartate (NMDA) receptors. However, it appears that gp120 and glutamate act synergistically to induce toxicity (220). A further test of the association between gp120 toxicity and NMDA receptors showed that an NMDA antagonist, 1-amino-3,5-dimethyladamantine (Memantine), could block the toxicity of gp120 (219). Antagonists to the NMDA receptor, such as D-2-aminophosphonovalerate, also inhibit toxicity of nonviral factors secreted by HIV-1-infected monocytes and macrophages (137). These experiments, however, do not prove that gp120 needs to bind directly to the NMDA receptor. Mechanisms that explain toxicity could involve other molecules that interact with gp120 at sites proximal to the NMDA receptor. In experiments with rat fetal brain cell cultures, gp120 was not toxic by itself but only in combination with cell culture fluids contaminated by mycoplasmas or lipopolysaccharide (27). The interaction between HIV-1-infected macrophages or monocytes and glial cells, particularly astrocytes, did elicit toxic effects of TNF- α and IL-1 β . The synthesis of these cytokines was also linked to release of arachidonic acid

metabolites from astrocytes (134). Such cell-mediated neuronal injury could result from release of gp120 from infected macrophages and subsequent interaction of this gp120 with astrocytes. Molecules such as vasoactive intestinal peptide which inhibit gp120-related neuronal toxicity may do so by competing with gp120 for binding to neurons and astrocytes. Clearly, there are multiple pathways by which HIV-1 proteins may act on the CNS.

Role of Cytokines in Normal Physiological Responses

Cytokines traditionally have been thought of as factors and intercellular signals confined strictly to cells of the hematopoietic system. However, there is now a large body of literature that demonstrates that the CNS and possibly the peripheral nervous system utilize cytokine cascades in normal physiology and in pathologic states. These cytokines can originate from resident cells of the nervous system, specifically, astrocytes and microglial cells, or from cells of the immune system that traffic through the CNS (Fig. 3). The targets of the cytokines within the CNS include cells of both neuronal and glial origin (Fig. 3). Similarly, resident cells of the nervous system may elaborate cytokines that target cells of the immune system that traffic through the CNS (Fig. 3).

While there is a great deal of *in vitro* evidence that TNF- α , IL-1 β , and IL-6 are secreted by both astrocytes and microglial cells, relatively little is known about the role of cytokines in normal physiologic signaling and communication between cells of the CNS (Fig. 3). In the developing rat nervous system, microglial cells are a major source of IL-1 β in the perinatal period (138). Given the observation that IL-1 β is an astroglial growth factor, it has been proposed that microglia may regulate astroglial growth during maturation of the nervous system. TNF- α similarly has been implicated to have a role in brain development (385). In the mature nervous system, much of the work on cytokines has focused on their role in modulating the hypothalamus. IL-1 β , TNF- α , and IFN- γ all exhibit intrinsic pyrogenic activity by acting directly on the thermoregulatory centers of the anterior hypothalamus (372). This endogenous pyrogenic activity is mediated by prostaglandin E_2 synthesis within the hypothalamus (58). IL-1 β is also able to provide feedback to the immune system indirectly by stimulating the murine hypothalamic-pituitary-adrenal axis, leading to increased production of corticotropin-releasing factor and subsequent secretion of immunosuppressive glucocorticoids (355). Excitation of the sympathetic pathway, which also originates in the hypothalamus and has nerve terminals in lymphatic organs, is yet another proposed mechanism by which IL-1 β is able to provide feedback to the immune system (180). Lastly, IL-1 β may also exert influence on satiety and the sleep-wake cycle, again by acting at the level of the hypothalamus (92). In the peripheral nervous system, very little is known about the role cytokines play. However, one study did demonstrate that non-neuronal cells of the rat sciatic nerve produce markedly increased levels of nerve growth factor in the presence of IL-1 β (218).

Role of Cytokines in Injury and Infection

In response to injury and infection, cytokine production within the CNS has been proposed to cause a myriad of changes. The changes that may have some relevance to HIV-1 infection can be summarized as follows. (i) In bacterial meningitis, TNF- α is produced by infiltrating macrophages and resident macrophages of the meninges, achieving

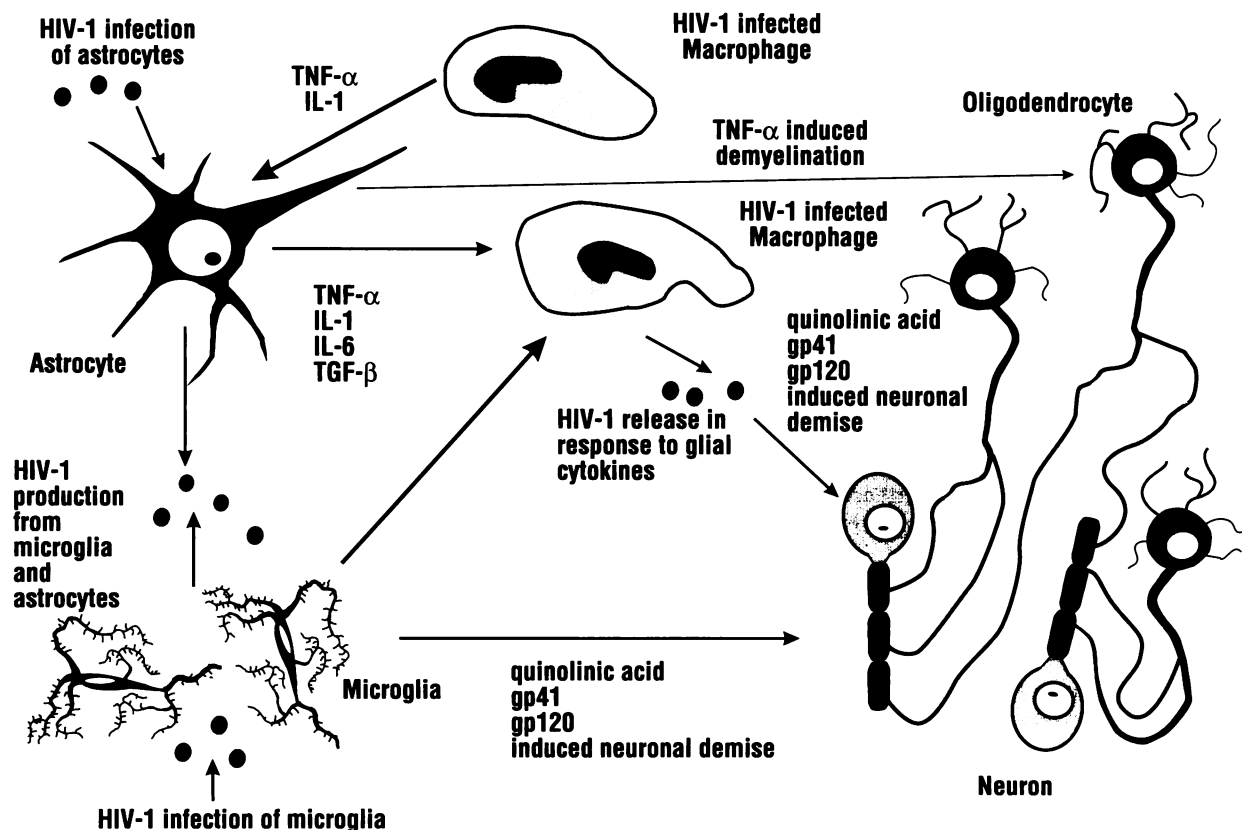


FIG. 3. Proposed roles of cytokines in the pathogenesis of HIV-1 infection of the nervous system. HIV-1 most likely enters the CNS in an infected macrophage. Microglial cells and astrocytes may then become infected with HIV-1. $\text{TNF-}\alpha$ and IL-1 secreted by the macrophage can amplify HIV-1 multiplication in microglia as well as reactivate HIV-1 from latently infected astrocytes. $\text{TNF-}\alpha$, IL-1, and IL-6 produced by microglia and astrocytes may amplify HIV-1 multiplication in macrophages. $\text{TGF-}\beta$ secreted by astrocytes may recruit additional macrophages into the region. Microglia and macrophages release toxic viral components and quinolinic acid that can damage neurons. This cycle of immune activation within brain parenchyma most likely leads to an increased viral burden in the brain as well as to the broad spectrum of neurological disease caused by HIV-1 infection of the brain.

levels detectable in the CSF (368). $\text{TNF-}\alpha$ causes a breakdown of the blood-brain barrier with resultant meningeal and parenchymal edema and further leukorrhea (259). Viral meningitis, in contrast, is not associated with elevated levels of $\text{TNF-}\alpha$ (211). (ii) In vitro, $\text{TNF-}\alpha$ induces oligodendroglial demise (311), and in vivo, $\text{TNF-}\alpha$ -positive cells (astrocytes and macrophages) have been found at the edge of multiple sclerosis plaques (163), suggesting that $\text{TNF-}\alpha$ -producing cells may play a role in demyelinating diseases. (iii) $\text{TNF-}\alpha$ is also able to induce expression of major histocompatibility complex class I proteins on astrocytes and oligodendrocytes, potentially exposing these cells to the toxic effects of trafficking cytotoxic T cells (241). (iv) Lastly, $\text{TNF-}\alpha$ and IL-1 β have been demonstrated to promote astrocyte proliferation (207). The role of these four mechanisms in the neuropathogenesis of HIV-1 infection is discussed below.

In Vivo Evidence for the Role of Cytokines in HIV-1-Associated Neuropathology

In 1989, Gallo and colleagues (119) examined the CSF of 38 HIV-1-infected patients for evidence of cytokine activation. Fifty-eight percent of the patients had elevated IL-1 β levels, 42% had elevated IL-6 levels, and none had detectable IL-2 levels. The elevations of IL-1 and IL-6 were not correlated with clinical signs of CNS involvement. Interest-

ingly, the investigators were unable to detect elevated CSF $\text{TNF-}\alpha$ levels in any of these patients, including 16 patients with opportunistic infections. While a second group also failed to detect $\text{TNF-}\alpha$ in CSF of 28 HIV-1-infected individuals (336), a third group found that 25 of 45 patients had elevated CSF levels of $\text{TNF-}\alpha$ (146). The discrepancy between the findings of these groups has been ascribed to technical differences in measuring $\text{TNF-}\alpha$. Grimaldi and colleagues also found that elevation of CSF $\text{TNF-}\alpha$ levels correlated with the presence of opportunistic infection of the CNS (146). The $\text{TNF-}\alpha$ levels were higher in CSF than in serum, further suggesting intrathecal production of the cytokine. No correlation was found between elevated $\text{TNF-}\alpha$ levels and the presence of HIV-1-associated dementia. In a study of pediatric AIDS encephalopathy (256), 11 of 26 children had elevated CSF $\text{TNF-}\alpha$ levels, but again, no correlation was found with the presence of progressive encephalopathy. Interestingly, elevated serum $\text{TNF-}\alpha$ levels were associated with the presence of encephalopathy, suggesting that circulating $\text{TNF-}\alpha$ may be responsible for the leukoencephalopathy associated with pediatric progressive encephalopathy.

The evidence from CSF studies clearly indicates that HIV-1 infection is associated with activation of the cytokine cascade in the meninges. However, while the CSF findings are an accurate reflection of meningeal pathology, they do

not necessarily reflect pathology of the parenchyma. This is particularly true for HIV-1 infection, in which the majority of the parenchymal pathology is subcortical and therefore not directly accessible to the CSF. Tyor et al. (363) examined frozen sections taken at the time of autopsy of the cortex and white matter of HIV-1-seropositive patients. They found that microglial cells (and to a much lesser degree, astrocytes) were frequently TNF- α positive by immunocytochemistry. IL-1 β and IFN- γ were detected in virtually all endothelial cells, while TNF- α - and IL-6-positive endothelial cells were less frequently seen. Interestingly, this group also found that five of seven patients had increased TNF- α levels in the CSF, but again no correlation was found with the presence or absence of CNS involvement. In contrast to Gallo's observation, none of the patients examined in this study had detectable CSF IL-1 β levels. In addition, major histocompatibility complex class II-positive CD4⁺ and CD8⁺ cells were identified in a perivascular location in the CNS and cited as further evidence that the immune system is activated in the neural parenchyma during HIV-1 infection.

In total, these studies suggest that the cytokine cascade is activated in the meninges and parenchyma of HIV-1-infected patients.

In Vitro Evidence for the Role of Cytokines in HIV-1-Associated Neuropathology

Using rat brain cultures, Merrill and colleagues (251) examined the ability of HIV-1 to induce TNF- α and IL-1 β . Both a macrophage-tropic and a T-cell-tropic HIV-1 strain induced both cytokines in astrocytes and microglial cells. Productive infection failed to occur, demonstrating that cytokine activation occurs independently of infection in these cells. Heat-inactivated virions, recombinant gp160, and gp41 induced TNF- α and IL-1 β , again demonstrating that infection was not a prerequisite for cytokine induction. Similarly, antibodies to epitopes in the gp120 and gp41 proteins of the envelope protein blocked the induction.

These results are similar to those of Sundar and colleagues (354), who found that intracranial injection of gp120 in the rat CNS resulted in detection of IL-1 β in the neural parenchyma. The IL-1 β elevation was associated with increased plasma steroid levels and a decrease in cell-mediated immune response. As discussed in a previous section, IL-1 β may have caused the steroid elevation by acting at the level of the hypothalamus in the hypothalamic-pituitary-adrenal axis. When gp120 was infused with alpha-melanocyte-stimulating hormone, a biologic blocker of IL-1 β activity, the steroid elevation was blocked.

The results of Merrill and Sundar are in contrast to those of Genis and colleagues (134), who used human glial cultures (both primary and cell lines). They found that HIV-1-infected monocytes cocultured with astrocytes released elevated levels of TNF- α and IL-1 β . However, in this case the monocyte was demonstrated to be the source of the cytokines. Furthermore, the addition of gradient-concentrated viral particles to the astrocytes failed to induce any cytokines. Genis et al. also demonstrated that a viable monocyte-astrocyte interaction was required for induction of the cytokines and that this induction is mediated by arachidonic acid metabolites.

As mentioned in an earlier section, Tornatore and colleagues (361) demonstrated that HIV-1 is able to infect human fetal astrocytes, establishing a persistent state of infection in which HIV-1 expression is undetectable. How-

ever, when the persistently infected astrocytes were cocultivated with a T-cell line, a productive phase of infection was reestablished. The ability to reestablish productive infection in the absence of cell-to-cell contact with the T-cell line implicated a soluble factor as a mediator of this induction. TNF- α and IL-1 β alone were subsequently found to induce the productive infection.

Similarly, Swingler and colleagues (356) found that, in cultures of human astrocyte cell lines and primary murine astrocytes, both transfected with an HIV-1 LTR-chloramphenicol acetyltransferase construct, TNF- α and IL-1 β activated the LTR-driven gene expression. IL-6 activated the LTR only in the murine cultures, while interferons generally suppressed expression of the LTR. TNF- α and IL-1 β induced an NF- κ B-like protein in a neuroblastoma and an astrocytoma cell line, respectively. The protein-bound sequences matching the enhancer of HIV-1 demonstrate that, similar to cells of the lymphatic system, cytokine induction of HIV-1 expression is mediated by NF- κ B in brain-derived cells (356).

These two studies suggest that, in the setting of cytokine induction, the viral burden of the CNS may be amplified by the induced expression of HIV-1 from infected resident cells of the nervous system.

Vitkovic and colleagues demonstrated that media conditioned by either primary rat or human astrocytes or glioma cell lines were capable of stimulating the expression of HIV-1 in a chronically infected promonocyte cell line (365). The medium from human cells did not contain TNF- α , nor did an antibody to TNF- α block the expression of HIV-1 by this medium. The medium did, however, contain detectable IL-6 levels, and an antibody to IL-6 blocked the expression of HIV-1 in the monocytes. These results suggest that HIV-1-infected monocytes that gain access to the CNS may have viral expression augmented by CNS-derived cytokines. This augmentation would further contribute to the high viral burden seen in the CNS of HIV-1-infected individuals.

Wahl and colleagues (369) found that the subcortical white matter of four patients with AIDS contained astrocytes and mononuclear cells that expressed transforming growth factor β (TGF- β). While TGF- β expression was closely associated with areas of apparent tissue pathology, expression was not limited to HIV-1-infected cells, implicating an alternative mechanism for induction of this cytokine. In vitro, HIV-1-infected monocytes released a soluble factor that promoted TGF- β secretion from noninfected neonatal rat astrocytes. Given that TGF- β is a chemotactic signal for monocytes, the authors of this study hypothesized that subcortical astrocytes use TGF- β to provide a signal for the ingress of monocytes into the CNS. The ingress of the monocytes leads to further astrocyte TGF- β production and possibly a self-perpetuating cycle of monocyte invasion.

Opportunistic Infections

Several opportunistic pathogens contribute to the neuropathology of AIDS. In most cases the neuropathology associated with other viral infections, parasitoses, mycoses, and bacterial infections in the CNS can be distinguished from HIV-1-associated neuropathology. A complete treatment of the neuropathology of the broad range of opportunistic infections complicating AIDS is beyond the scope of this review. The reader is therefore referred elsewhere for this information (1, 111, 144, 227).

DIAGNOSTIC STUDIES OF HIV-1 ENCEPHALOPATHY

Neuropsychological Tests

The pattern of neuropsychological performance deficits and reported changes in cognition, motor function, and behavior are consistent with a subcortical dementing process (247). The most reliable decrement in performance among AIDS patients has been on measures with a substantial motor and psychomotor speed component, although Skorszewski and colleagues (340) observed that the overall pattern of impairment among AIDS patients includes such higher cortical functions as abstraction, memory, and verbal spontaneity. Others have suggested that HIV-1-induced cognitive dysfunction manifests with more variability, including dementia with cortical deficits, subcortical dementia, and subcortical cognitive deficits in the absence of global intellectual deterioration (86).

A review of 14 neuropsychological investigations with AIDS-related complex or AIDS patients suggests that language functioning, general knowledge base, and visuospatial-visuoconstructive abilities are spared, while motor and psychomotor tasks, particularly those with a timed component, are reliably impaired (90, 223, 255, 307, 340, 362, 364). Indeed, performance deficits were observed for the WAIS-R Digit Symbol subtest in nine of nine studies, for the Grooved Pegboard in four of four studies, and for Finger Tapping in two of three studies. Memory represents a diverse array of processes, with attention being a *sine qua non*. AIDS patients frequently present with complaints of concentration difficulties; however, performance deficits have not typically been detected on attentional measures. Variable findings have been reported for verbal and nonverbal memory. Researchers have suggested that discrepant findings may be the result of differences in tests (348) and/or due to failure to examine the component parts of memory. Perdices and Cooper (287) observed that learning rate and capacity as well as the complexity and modality of material were important determinants of the outcome of performance on tests of memory. Their results indicated that learning rate was unimpaired regardless of the complexity or modality of the material. Learning capacity was normal for simple, cued verbal learning but impaired for more complex material, either verbal or nonverbal. Thus, while it appears that memory may be affected in some AIDS patients, the precise functional breakdown remains unelucidated.

Executive functioning encompasses a diverse array of functions, including monitoring, directing, and controlling behavior, abstract reasoning and concept formation, and mental flexibility, as well as aspects of personality. Consequently, adequate performance on diverse tasks relies on the integrity of this complex system. This area has not received adequate attention in AIDS investigations; thus, conclusions with regard to which aspect, if any, of executive functions are affected must be tentative. Significant differences between AIDS patients and HIV-1-seronegative controls have been noted for various tests that assess mental flexibility and set shifting (178, 287, 348, 364). Performance deficits on the WAIS-R Similarities subtest suggest that verbal concept formation and novel problem-solving may be adversely affected (364). Increased empirical evaluation of the various components of executive functioning is warranted.

CSF

CSF studies show a mononuclear pleocytosis in one-fifth of individuals with HIV encephalopathy and increased CSF

protein in two-thirds (303), and the protein levels are typically below 200 mg/dl (265). Intrathecal synthesis of HIV-1-specific antibody and oligoclonal bands can be demonstrated frequently (308) but may not be predictive of the CNS disease (141). Although some studies have indicated that the presence of CSF HIV-1 p24 antigen is associated with a progressive encephalopathy in children (101, 143) and in some adults (142), subsequent studies have failed to confirm that the detection of CSF HIV-1 antigen predicts subsequent neurological deterioration (38, 296). Similarly, the isolation of HIV-1 from CSF is not a useful marker for HIV-1 encephalopathy (38). The mononuclear pleocytosis observed is generally low, usually with counts of <50 cells per mm^3 (265). Cytological analysis may reveal reactive lymphocytes, plasma cells, and, in rare instances, multinucleated giant cells (185). The CSF glucose is normal or borderline. Antibody in the serum should be detectable by the time the patient presents with HIV-1 encephalopathy, but both adults (303) and children (305) may present with the encephalopathy before seroconversion.

Cytokines can be detected in the CSF of patients with HIV-1 infection. As discussed earlier, in a study by Gallo and colleagues (119), IL-1 β was found in the CSF of 58% of patients with HIV-1 infection and IL-6 was found in 42%. Both cytokines could be detected in the absence of clinical neurological disease but appeared to be detected more frequently in the presence of HIV-1 encephalopathy (119). Other cytokines that are detected in elevated levels in the CSF of some patients with AIDS include the macrophage products TNF- α , neopterin, and β_2 -microglobulin and the T-cell products soluble CD8 and gamma interferon (363). In one small series (240), TNF- α appeared more commonly in patients with moderate to severe HIV-1 encephalopathy than in those with mild disease. However, other investigators have failed to find TNF- α in the CSF of patients with HIV-1 encephalopathy (120). These discrepancies may simply reflect the sensitivity of the assays used.

Elevated β_2 -microglobulin, a low-molecular-weight protein that is bound to the major histocompatibility protein and expressed on the cell surface of almost all nucleated cells, has been detected in the CSF and is more common in the presence of neurological disease (30, 31, 96, 240). CSF β_2 -microglobulin levels do not appear to be proportional to the degree of CSF pleocytosis or to an alteration in the blood-brain barrier (30). Brew and colleagues argue that its concentration is a useful surrogate marker for the severity of HIV-1 encephalopathy (30, 31). McArthur and colleagues contend that a level of CSF β_2 -microglobulin of >3.8 mg/liter occurring in the absence of opportunistic infection is a clinically useful marker for HIV-1 encephalopathy (243).

Quinolinic acid, a potent neuroexcitant in the CNS (351) which has also been suggested as a pathogenic mechanism in AIDS dementia complex (158, 159, 204), is induced in macrophages infected with HIV-1, human herpesvirus 6, and alpha interferon (32). Increased levels of CSF quinolinic acid have been associated with poorer neuropsychological performance across the spectrum of HIV-1-associated neurological disease (158, 159, 204). Some investigators have found myelin basic protein in the CSF of patients with HIV-1 encephalopathy and have related its presence to the associated demyelinating process (240). Conversely, in asymptomatic HIV-1-infected individuals with intrathecal synthesis of immunoglobulin G, Marshall and colleagues (234) were unable to detect CSF myelin basic protein. However, others (389) detected it in two patients with HIV-1 encephalopathy, both of whom had advanced and rapidly progressive disease.

A potentially useful observation for differentiating neurological disease resulting from HIV-1 from that due to CNS opportunistic infection in HIV-1-infected patients is the demonstration of calprotectin, a protein with calcium-binding and antimicrobial properties, in high concentrations in the CSF of HIV-1-infected patients with opportunistic CNS infections in contrast to levels in the reference range with HIV encephalopathy (91).

Radiographic Studies

The chief value of radiographic imaging of the brain in patients with suspected HIV-1 encephalopathy is in ruling out other neurological disorders (301). These studies, chiefly, computed tomography of the brain (CT scan) and cranial magnetic resonance imaging (MRI), are otherwise often unrewarding (25). Likewise, routine screening of neurologically asymptomatic HIV-1-infected individuals has a low yield for the detection of features suggestive of HIV encephalopathy (298). Unless contraindicated, CT scan of the brain should be performed with a technique that uses a double dose of contrast and delayed scan (297), a technique that increases the likelihood of detecting the lesions of toxoplasmosis.

The most commonly reported abnormality on CT scan of the brain is cerebral atrophy (39, 216, 265, 266). A correlation between neuropsychological function, namely, a slowing of response time and severity of brain atrophy determined by cerebral ventricular enlargement on CT scan (175) and on MRI (213), has been observed. Additionally, a correlation between brain atrophy on MRI and the presence of HIV in CSF and elevated levels of β_2 -microglobulin has been demonstrated (345). On CT scan, white matter lesions are infrequently observed, but their detection is increased dramatically by the increased sensitivity of MRI for white matter disease. Olsen and colleagues (279) noted that the most commonly observed pattern of white matter disorder visualized on MRI in HIV-1 encephalopathy was "diffuse," a widespread involvement of a large area. Less commonly observed patterns were characterized as "patchy," localized involvement with ill-defined margins, and "punctate," small foci of <1 cm in diameter (279). Mild brain abnormalities detected on cranial MRI, including slight brain atrophy, need not reflect the presence of underlying HIV encephalopathy (98) nor show progression over time (299).

Preliminary studies with positron emission tomography (PET), using [^{18}F]fluorodeoxyglucose (FDG), have defined the functional pathology of HIV encephalopathy in nine patients (316). The FDG-PET scans of these cognitively impaired individuals were analyzed by a mathematical model of regional metabolic interactions referred to as the subprofile scaling model (258). Assessment of the regional cerebral metabolic rate for glucose demonstrated relative subcortical (thalamus and basal ganglia) hypermetabolism in early HIV-1 encephalopathy and cortical and subcortical gray matter hypometabolism in advanced stages of the disease (316). The alterations in subcortical metabolism appear to correlate with impairment of fine-motor control, and those of cortical metabolism correlate with impairments in verbal fluency and problem-solving. Investigators have suggested that FDG-PET may be a useful objective means of demonstrating the onset of HIV-1 encephalopathy and also provides a means of following response to antiviral therapy (316). A study of cerebral blood flow with the use of single-photon emission tomography with $^{99\text{m}}\text{Tc}$ -hexmethyl propyleneamineoxime in two AIDS patients with cognitive

disturbances revealed bilateral cerebral blood flow loss in the temporal lobes in one patient and in the temporal and parietal lobes in the other patient (95). Utilizing [^{123}I]IMP single-photon emission tomography, Schielke and colleagues (324) reported similar results in patients with early HIV-1 disease, and Masdeau and colleagues (237) found analogous perfusion defects in a comparable group of patients. These findings regarding cerebral perfusion in HIV-1 encephalopathy may not be valid in patients with a history of cocaine and polydrug use (167). Single-photon emission tomography and PET have been proposed as potentially useful methods to study the progression of HIV-1 encephalopathy (203).

Lastly, as a correlate of the neuronal loss detected with quantitative morphometry, studies employing proton magnetic resonance spectroscopy reveal significant reductions in levels of *N*-acetyl aspartate relative to creatine and elevations in choline-containing compounds relative to creatine in patients with moderate to severe HIV-1 encephalopathy (249). *N*-Acetyl aspartate is a metabolic marker for normal neuronal function, and its decrease relative to creatine suggests neuronal loss in this disorder. The alteration of the choline/creatine ratio is possibly the result of changes in membrane metabolism (249).

Electrophysiological Studies

A wide variety of studies have attempted to correlate neurophysiological studies with the presence or degree of HIV-1 encephalopathy. The earliest studies employed electroencephalography (EEG). Some investigators have suggested that the EEG is a sensitive method of detecting subclinical cerebral disease in HIV-1-infected individuals (99) which could be correlated with clinical illness (21). Tinuper and colleagues (360) found no definitely abnormal EEG tracings in neurologically asymptomatic, HIV-1-infected individuals, but they detected "borderline" abnormalities in 33% which they thought required prospective evaluation. In another series, the most common EEG abnormality seen was an increased amount of generalized episodic or persistent, predominantly anterior, slow wave activity (99, 117). Other abnormalities included a lower maximal amplitude of dominant background activity and more marked generalized and anterior disturbances on EEG in early HIV-1 infection compared with uninfected controls (99). However, in a series from the multicenter AIDS cohort study, no EEG abnormalities could be attributed to HIV-1 infection in otherwise asymptomatic individuals (274). Computerized spectral analysis of the EEG has also been used in this regard (173, 281, 282) and may be more sensitive than routine EEG (282).

Other electrophysiological techniques that have been used to study HIV-1 encephalopathy include brain stem auditory evoked potentials and event-related brain potentials. Brain stem auditory evoked potential studies have detected significant delays in waveforms I-V and III-V in HIV-1-infected individuals compared with controls, indicating abnormalities in the upper brain stem (280, 315). Multiple regression analysis in those studies has failed to reveal a significant influence of other factors, such as medical history or drug use, on these waveforms (94). Studies employing cognitive event-related potentials have also shown a delayed response time (8, 278), suggesting their value in detecting early cognitive disease. However, like EEGs, these studies still remain unproven predictors of the presence or progression of HIV-1 encephalopathy.

TREATMENT

The first effective antiretroviral agent for HIV-1 infection was zidovudine (azidothymidine). Pharmacodynamic studies of zidovudine reveal that, in patients given 5 mg/kg intravenously every 4 h, CSF levels may briefly exceed 1 μ mol/liter (196). The CSF-to-plasma ratios vary between 135% following an oral administration of 15 mg/kg to 15% at an oral dose of 2 mg/kg (196). However, brain tissue levels may not be adequately reflected by CSF levels of the drug. In AIDS patients treated with this antiretroviral agent, extracellular hyaline globules that show the presence of zidovudine isomers on high-performance liquid chromatography have been detected in the white matter of the brain and spinal cord (10).

In light of its penetration of the blood-brain barrier and efficacy as an antiretroviral agent, it is not unexpected that zidovudine might prove effective in the treatment of patients with HIV-1 encephalopathy. Indeed, a decline in the overall incidence of HIV-1 encephalopathy was noted after the introduction of zidovudine (295). Initial anecdotal clinical reports (166, 281) demonstrated improvement in HIV-1 encephalopathy in adults with zidovudine use. These impressions were shortly confirmed by more comprehensive studies (325). Both the smaller study by Price and colleagues (302) and the larger one by Schmitt and colleagues (325) showed only partial improvement in neuropsychological abnormalities associated with HIV-1. Parallel studies of the effect of zidovudine on brain metabolic abnormalities with HIV-1 encephalopathy have demonstrated that large focal cortical abnormalities of glucose utilization detected by PET utilizing FDG could be reversed (35) and that CSF β_2 -microglobulin decreases (31). Further studies to confirm the value of zidovudine in this condition may be difficult to perform because of its early use in the course of infection. An interesting observation by Helbert and colleagues was the appearance of an acute meningoencephalitis in 4 of 21 patients with AIDS or AIDS-related complex within 17 days of dose reduction of zidovudine because of myelotoxicity (157). Three of the four patients had prior evidence of HIV-1 encephalopathy (157).

In children, a similar and perhaps more dramatic improvement in encephalopathy was demonstrated by Pizzo and colleagues with the use of continuous-infusion zidovudine (291). In that study, neuropsychological improvement occurred in all patients with evidence of HIV-1 encephalopathy prior to the administration of zidovudine, and in some, the improvement was noted despite the absence of improvement in immunological parameters (291). The optimal intravenous dose of zidovudine in children appeared to be between 0.9 and 1.4 mg/kg per h (291).

Whether other antiretroviral therapies will prove as effective as zidovudine in the treatment of HIV-1 encephalopathy remains unanswered. Neither dideoxyinosine nor dideoxycytosine appears to cross the blood-brain barrier as well as zidovudine. Drugs that do not have a primary effect on HIV-1, such as CNS stimulants (methylphenidate and dexedrine) and corticosteroids, have been used in a limited and nonrigorous fashion in attempts at symptomatic improvement of HIV-1 encephalopathy. Anecdotally, prednisone has been reported to improve HIV-1 encephalopathy in children (349). No data are available regarding its value in adults with this disorder. Although there are legitimate concerns relative to the potential deleterious effect of corticosteroids on HIV-1-infected patients with an already compromised immune system, one study of HIV-1-infected

children receiving prednisone showed no consistent or significant change in the number or percentage of CD3, CD4, CD8, or CD19 lymphocytes (322).

CONCLUSIONS

The ability of HIV-1 to infect and destroy cells of the host immune system is of paramount importance in the pathogenesis of AIDS. The principal cause of death in AIDS patients is due to complications associated with the uncontrolled multiplication of opportunistic pathogens that manifest themselves in the presence of a weakened immune system. Although opportunistic infections also give rise to neurological complications associated with AIDS, in general, these pathologies are separable from HIV-1-associated neuropathology. This is apparent when one considers that HIV-1-associated neurological disease can occur in the absence of opportunistic infection.

A broad spectrum of neuropathological findings, which includes diffuse damage to white matter with myelin loss, reactive astrogliosis, thinning of the neocortex, loss of synaptic density, and vacuolation of dendritic processes, is associated with HIV-1 infection in the CNS. In vivo evidence of direct HIV-1 infection of neural cells has been limited. Virus is most often detected in macrophages that have invaded brain parenchyma or in microglial cells. Since it is hard to imagine how direct virus multiplication in macrophages and microglial cells can give rise to the broad spectrum of neurological disease just described, indirect mechanisms of damage to neural elements have been proposed. Damage caused by a variety of virally encoded proteins, including Nef, Tat, gp41, and gp120, has been proposed to contribute to HIV-1-associated neuropathology. In addition, damage caused by the elaboration of TNF- α by macrophages, microglia, and astrocytes has been proposed to cause the demyelination of neurons in the CNS. Macrophages and microglial cells also have been shown to secrete quinolinic acid, a potent neurotoxin, which may also damage neurons. Elaboration of TNF- α , IL-1 β , and IL-6 by astrocytes and microglia may act to amplify HIV-1 multiplication in infiltrating macrophages. Conversely, TNF- α and IL-1 β released by macrophages may act to amplify HIV-1 multiplication in microglial cells and to reactivate HIV-1 in latently infected astrocytes.

The extent to which each of these mechanisms damages nervous system elements is far from clear. There may, in fact, be additional mechanisms of damage that have either eluded investigators or simply received little attention. For example, the elaboration of toxic components of the complement system are known to cause bystander injury to cells surrounding inflamed tissue. It is possible that some of these components are elaborated in the CNS by infiltrating cells of the immune system or perhaps by resident cells in the CNS such as microglial cells. The roles of natural killer cells and cytotoxic T cells in HIV-1 infection in the CNS are also not known. As we learn more about the control of immune reactivity in the CNS environment, we will no doubt gain a better understanding of how viruses such as HIV-1 cause neurological disease.

The mechanism by which HIV-1 gains access to the CNS is also not known. Since HIV-1 is a highly cell-associated virus, it most likely gains access to the CNS in an invading cell of the immune system. A variety of immune system cells have been shown to routinely cross the blood-brain barrier, and these include T cells, B cells, and macrophages. The signals that regulate this immune system traffic in and out of

the CNS are not well understood. All of the evidence to date favors HIV-1 entering the CNS in macrophages. However, one cannot rule out the possibility that the virus may also gain access to the CNS in an infected T cell.

One of the earliest manifestations of CNS involvement in HIV-1-infected patients is an acute meningitis or meningoencephalitis. HIV-1 presumably first gains access to the meninges in an infected monocyte or macrophage. This probably results in further infection of other mononuclear cells in the meninges and leads to the elaboration of cytokines, toxic viral products, and perhaps complement components, all of which may contribute to these meningoencephalitis. Involvement of brain parenchyma probably is initiated by HIV-1-infected macrophages or perhaps even HIV-1-infected T cells crossing the blood-brain barrier. The presence of infiltrating cells of the immune system in brain parenchyma most likely leads to damage by the elaboration of cytokines and other nonspecific factors which damage cells. Resident cells of the nervous system may then be infected with HIV-1, leading to their destruction or interfering with their normal functions in the CNS. The presence of cytokines such as TNF- α , IL-1 β , and IL-6 in the CNS most likely leads to microglial activation and astroglial proliferation. Microglial cells and astrocytes also elaborate TNF- α , IL-1 β , and IL-6 and contribute to the overall state of activation of infiltrating immune system cells and resident glial components. The enhanced state of activation probably leads to more efficient viral replication and further tissue damage. This resulting pathology probably also leads to expression of TGF- β by subcortical astrocytes, which attracts more macrophages to the site of injury. The continued production of cytokines, toxic viral components, and perhaps other nonspecific toxic factors such as complement in the subcortex could lead indirectly to neuronal and oligodendroglial destruction which is manifested as AIDS-associated cognitive-motor complex.

Damage to the nervous system in AIDS is obviously multifactorial. Each of the mechanisms described above may play a significant role in HIV-1-associated CNS disease. The extent to which direct infection of resident CNS cells plays a role will have to await the application of more sensitive techniques such as in situ polymerase chain reaction. This will undoubtedly help in clarifying the precise role of these cellular elements in HIV-1-associated neuropathology.

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