HIV-1 Associated Dementia: Clinical Features and Pathogenesis

Christopher Power and Richard T. Johnson

ABSTRACT: HIV-1 infection is characterized by multiple neurological syndromes occurring at all stages of infection. HIV-1-associated dementia, however, is the most devastating CNS consequence of AIDS because of its poor prognosis and functional impairment. A clinical triad of progressive cognitive decline, motor dysfunction, and behavioural abnormalities typifies this subcortical dementia which eventually affects 15 to 20% of AIDS patients. Neuroimaging, CSF studies and neuropsychological testing are frequently required in diagnosing HIV-associated dementia, to exclude other conditions including psychiatric illnesses, opportunistic diseases and systemic disorders. The pathogenesis of HIV dementia is uncertain and there is evidence that multiple mechanisms of neurological injury occur. These mechanisms include: the role of neurovirulent strains of HIV; the potential neurotoxicity of HIV gp120, nitric oxide and quinolinic acid; immunologically mediated CNS injury through the action of cytokines and arachidonic acid metabolites; and altered blood-brain barrier permeability. A collective approach involving clinical studies, in vitro assays and animal models will provide greater insight into the pathogenesis and the rational development of therapy for HIV dementia.

Over the past decade, the AIDS pandemic has rapidly expanded worldwide resulting in at least 13 million people being currently infected with either HIV-1 or HIV-2.¹ Both HIV-1 and HIV-2 belong to the lentivirus family of retroviruses and like other lentiviruses such as simian and feline immunodeficiency viruses, are characterized by persistent infection and immune deficiency resulting in death.²⁵ Although both HIV-1 and HIV-2 are associated with immune suppression and CD4-positive lymphocyte depletion, HIV-1 appears to be more virulent, causing a more rapid progression of disease, has a wider geographical distribution, generates a broader genetic diversity and possibly is associated with a larger range of clinical phenotypes although the neurological syndromes accompanying HIV-2 infection have not been clearly defined.⁶⁻¹⁰ Early in the AIDS epidemic it was apparent that neurological disease was a common feature at all stages of HIV-1 infection in both children and adults.¹¹⁻¹³ The spectrum of neurologic disease occurring in AIDS encompasses both primary HIV-induced illnesses such as aseptic meningitis, vacuolar myelopathy, diverse peripheral neuropathies, and HIV dementia (Figure 1) as well as secondary or opportunistic illnesses such as cerebral toxoplasmosis, cytomegalovirus (CMV) encephalitis, and cryptococcal menigitis.¹⁴ HIV-1 associated dementia (HIVD) is one of the most devastating complications of HIV infection because of its poor prognosis and the severity of the patients’ functional impairment. Consequently, HIVD has attracted attention because of the severity of clinical illness and the multiple mechanisms of pathogenesis proposed for this profound neurological syndrome. Many of the ideas and experimental techniques derived from the study of AIDS-related neurological diseases are applicable to other neurological diseases such as multiple sclerosis and Alzheimer’s disease.¹⁵ This article outlines the clinical features of HIV dementia and possible pathogenic mechanisms underlying its development.

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The syndrome demonstrates a marked diversity in its rate of advancement, as shown in Figure 2, but the factors that determine this variability in the disease course are uncertain. Cognitive slowing and ataxia may progress to complete mutism and paraparesis. Depression and psychosis can be mistakenly diagnosed in patients with HIVD, resulting in the initiation of inappropriate antidepressant or antipsychotic medications. It is important to rule out other causes of altered mental status. However, nonspecific abnormalities may occur in some patients with HIVD, making it difficult to distinguish this syndrome from psychiatric illness or opportunistic infections of the CNS. The clinical status of each patient was assessed at the time of initial diagnosis of HIVD and the final evaluation before death.

Laboratory Investigations

Additional diagnostic tests include CSF and radiological studies to rule out other causes of altered mental status. However, nonspecific abnormalities may occur in some patients with HIVD, making it difficult to distinguish this syndrome from psychiatric illness or opportunistic infections of the CNS. The clinical status of each patient was assessed at the time of initial diagnosis of HIVD and the final evaluation before death.

Neuropsychology

HIV dementia has a characteristic neuropsychological profile with progressive decline in performance, at least two areas including motor speed, nonverbal memory, and frontal lobe tasks. Because it is essential to diagnose an altered mental status in AIDS patients as early as possible, neuropsychological testing is not universally available. A brief quantitative diagnostic test was developed, the HIV Dementia Scale (HDS). It is used in conjunction with other diagnostic tests. This scale tests specific abilities including timed motor tasks, frontal lobe functions, and memory that are impaired early in HIV infection (Figure 3). The HDS is easily administered at the bedside with superior sensitivities and specificities to other short mental status assessments such as the Mini-Mental Status Examination. This test may also be of value in following patients’ cognitive status over time and response to therapy.
The HIV dementia scale (HDS) was designed to provide sensitivity and specificity to other bedside tests. A score of < 10 is a brief and easily administered diagnostic test that demonstrates superior sensitivity for detecting early disease and may be used to follow the course of dementia.36 Other features observed include multinucleated giant cells, diffuse myelin pallor, and microglial nodules and/or HIV antigens and genome.40-42  However, other neuropathological features have been observed more frequently in AIDS patients with dementia.18-36-37 Asymptomatic HIV-infected individuals may show some of these pathological changes and the presence of multinucleated giant cells and diffuse myelin pallor have HIVD although 50% of HIVD patients have neither multinucleated giant cells nor diffuse myelin pallor.36 In addition to neuronal loss, more sensitive morphological techniques have indicated that a loss of synaptic contacts and vacuolar changes in neurons in both the deep grey matter and cortex occur in patients dying with AIDS.44-56 There is a paucity of lymphocytes found in the brains of patients dying with AIDS unlike the CSF in which there is a lymphocytosis;38 thus, equating the CSF cell profile with the cell types and degree of inflammation found in the brain in patients with AIDS can be very misleading.

HIV Detection in Brain

HIV antigens and viral genome can be detected in the brains of AIDS patients45-47 primarily in the deep grey matter and white matter.48 A definitive correlation between viral burden in the brain and the severity of clinical neurological disease has not yet been shown. In fact, a striking dichotomy exists between the small number of HIV-infected cells and the severity of the clinical phenotype.49 The majority of cells infected in the CNS are microglia and perivascular macrophages45-50 but astrocytes have also been shown to be infected to a lesser extent, especially in children with HIV infection.51-52 Endothelia, oligodendrocytes and neurons have not been shown convincingly to be infected by HIV in vivo. The low levels of viral antigen and genome detection in the brains of AIDS patients may reflect the insensitivity of techniques such as immunocytochemistry or in-situ hybridization although newer technologies such as in-situ polymerase chain reaction (PCR) also do not demonstrate high levels of detectable viral genome in AIDS patients with and without HIVD compared to other CNS viral infections.53

### Table 1: Clinical features suggestive of HIV dementia.

| 1. | HIV-1 seropositivity and CD4 level ≤ 200 cells/mm³. |
| 2. | History of progressive subacute mental decline: apathy, memory loss, and slowed cognition. |
| 3. | Physical findings include slowed limb and eye movements, hyperreflexia, hypertonia, release signs and an HDS score of ≤ 10. |
| 4. | Neuropsychological testing demonstrates worsening performance in at least two areas including frontal lobe tasks, motor speed, and nonverbal memory. |
| 5. | CSF studies show elevated p24, IgG, and protein levels and the absence of other infections, i.e., cryptococcus and syphilis. |
| 6. | Cranial imaging reveals cerebral atrophy and white matter abnormalities including hyperintensities on MRI and hypodensities on CT; exclusion of opportunistic processes. |
| 7. | Exclusion of major psychiatric and metabolic disorders, and substance abuse. |

**Neuropathology**

Pathological features of HIV dementia observed by histopathological methods are striking for the lack of correlation between the severity of dementia and the inflammatory pathological changes.18,36,37 Asymptomatic HIV-infected individuals may show mild pathological changes and HIV antigens in the CNS early in infection.38,39 AIDS patients with and without HIV dementia may manifest HIV encephalitis which is defined by multiple foci of multinucleated giant cells and microglial nodules and/or HIV antigens and genome.40-42 However, other neuropathological features including diffuse myelin pallor and neocortical neuronal dropout have been observed more frequently in AIDS patients with dementia.18,36,43,44 Most patients with multinucleated giant cells and diffuse myelin pallor have HIVD although 50% of HIVD patients have neither multinucleated giant cells nor diffuse myelin pallor.36 In addition to neuronal loss, more sensitive morphological techniques have indicated that a loss of synaptic contacts and vacuolar changes in neurons in both the deep grey matter and cortex occur in patients dying with AIDS.44-56 There is a paucity of lymphocytes found in the brains of patients dying with AIDS unlike the CSF in which there is a lymphocytosis;38 thus, equating the CSF cell profile with the cell types and degree of inflammation found in the brain in patients with AIDS can be very misleading.

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**Treatment**

HIV dementia has been shown to improve transiently with antiretroviral therapy over a short time period. Zidovudine (AZT) appears to ameliorate signs and symptoms in adults with HIVD57-59 and children with AIDS-related delayed motor and cognitive development show improved performance with AZT therapy.60 Clinical trials testing other therapies including other nucleoside analogs, calcium channel blockers and inhibitors of TNF-alpha synthesis are in progress. The key issue in developing rational therapy for HIVD is a clear understanding of the pathogenesis underlying this clinical condition.
syndrome but the observation that HIVD is, in part, reversible provides optimism in considering therapeutic interventions.

**PATHOGENESIS**

In attempting to understand the mechanisms underlying the development of CNS disease associated with HIV infection, experimental approaches in the fields of neurobiology, immunology, molecular biology, and virology have been employed. Consequently, numerous hypotheses with supporting data from studies of both animal retrovirus models and humans in addition to *in vitro* cell culture techniques to explain the pathogenesis of HIVD have emerged over the past ten years. These hypotheses include roles for potential host and viral neurotoxic molecules, immunological molecules that are damaging to the CNS and the role of distinct viral strains in the development of HIV-related CNS disease. Each of these strategies will be reviewed but it is prudent to bear in mind that there are few correlative data between the results of *in vitro* assays and *in vivo* findings to date.

It is widely assumed but not documented that HIV gains access to the brain through infected blood-derived macrophages or monocytes that traverse blood-brain barrier whereupon susceptible adjacent cells (microglia and astrocytes) become infected. This proposed route of infection has been termed the Trojan Horse hypothesis and is supported by data indicating that many of perivascular cells observed in the brains of AIDS patients are HIV-infected macrophages. Cellular entry by HIV into blood-derived macrophages and T cells is dependent on the cell surface molecule, CD4, which acts as a receptor for HIV. But in the CNS, the picture is more complicated because in addition to CD4, other HIV receptors have been identified including the molecule, galactocerebroside, and putative receptors on astrocytes and endothelial cells.

**HIV Strain Diversity**

As with other viruses, the envelope protein of HIV participates in cellular entry and influences its tropism or which cells are infected. HIV cell tropism is dependent on specific sequences within the V3 region of the envelope. In the few patients from whom brain-derived HIV envelope sequences including the V3 region were obtained, a striking homogeneity in viral sequences was observed. This finding is in contrast to HIV blood-derived envelope sequences and strains which may vary widely depending on the stage of disease and the individual host. The brain-derived sequences of HIV resemble macrophage-tropic HIV strains and infection by live brain-derived isolates is restricted to macrophages *in vitro*. Thus, it is not surprising that principal cell infected in the CNS is the microglia which is of macrophage lineage. Macrophage tropism is, therefore, a necessary feature of an HIV strain to infect the CNS and subsequently cause disease.

Different retroviruses show a marked variation in their ability to infect the CNS (neurotropism) and cause neurological disease (neurovirulence) in animal models. Some animal lentiviruses such as simian immunodeficiency virus and Visna/Maedi are characterised by neurovirulent strains. To address the question of whether there are distinct sequences of HIV that are associated with neurovirulence, i.e., the ability to cause dementia, a study was performed comparing HIV envelope sequences from HIVD and non-demented AIDS patients. HIV proviral DNA was derived from autopsied brains of HIVD and control non-demented (ND) AIDS patients who were closely followed in the NeuroAIDS clinic postmortem at the Johns Hopkins Hospital. The HIVD and ND groups were matched for age, CD4 level, and antiretroviral therapy. Sequence analysis of the V3 and flanking regions of HIV envelope was performed. The brain-derived HIV sequences from all patients regardless of group resembled previously reported macrophage-tropic strains of HIV (Figure 4). Two positions, 305 and 329, in the 143 amino acid fragment encompassing the V3 region showed significant diversity between the two clinical groups (Figure 5). In addition, sequences derived from individuals with HIVD exhibited multiple residues at which unique amino acids relative to the non-demented group were identified. The unique amino acids were more frequently observed in the more severely demented patients. These results indicate that macrophage-tropic strains occur in the brains of all AIDS patients but, in addition, there are distinct HIV sequences related to the clinical development of HIVD. Whether these sequence differences are directly involved in the pathogenesis of
HIVD or merely linked to other neuroviral genes is unknown, however, it is of interest that peptides made from the V3 and flanking regions have been shown to be not neurotoxic in vitro although peptides derived from HIV strains associated with HIVD have not yet been evaluated.86 Tropism studies of recombinant infectious HIV clones bearing the brain-derived V3 regions from patients with and without HIVD revealed that these clones infected only macrophages and microglia, suggesting that HIV macrophage-tropism is an essential step in the development of neurovirulence.87 Further sequence analysis of other regions of the HIV genome and the reconstruction of HIV recombinant clones to be tested in vitro using different genomic regions of HIV may elucidate viral genetic determinants participating in the pathogenesis of HIVD.

Neurotoxicity
Potential host and viral neurotoxic molecules have been identified in association with HIV infection.88,89 The HIV gp120 envelope protein has been shown to the neurotoxic in different in vitro and in vivo systems.64,65 The means of neuronal injury and death may be direct or indirect although it appears to be a excitotoxic mechanism, being both calcium-dependent and mediated by glutamate (NMDA) receptors.66 gp120 neurotoxicity is reduced by both calcium channel blockers and glutamate receptor blockers which has led to a clinical trial in which different calcium channel blockers are being tested therapeutically in patients with HIVD. Other neurotoxic agents have been implicated in the pathogenesis of HIVD including quinolinic acid which is tryptophan-derived and has been shown to be elevated in the CSF of patients with HIVD62 and nitric oxide which appears enhanced gp120 neurotoxicity.91 Guilian et al. have identified a small molecule (<5000 kD) which has been shown to damage neurons in vitro and is secreted by HIV-infected macrophages and/or macrophages treated with gp120 peptide.66 An indirect mechanism of neurotoxicity seems most plausible in light of the small number of HIV infected cells in the CNS.

Neuroimmunology
Immunological activation is a feature of HIV infection both within and outside the CNS.88,92 Astrocytes and microglia appear activated early in infection93,94 and different immunological molecules produced by these cell types including cytokines and arachidonic acid metabolites show increased expression in vivo and in vitro in association with HIV infection.64,65,66 Wesselegh et al. have reported that increased transcription of TNF-alpha occurs in the brains of patients with HIVD with a strong correlation between level of TNF-alpha mRNA and severity of HIV dementia (Figure 6).64 Arachidonic acid metabolites are also elevated in the CSF of patients with HIVD and have been shown to be associated with HIV infection in glial cultures.96,97 To examine the influence of host genetic diversity on the susceptibility to immunological activation in the pathogenesis of HIVD, studies of HLA antigen expression in patients with and without HIVD are underway.

Blood Brain Barrier Alteration
The consequences of immunological activation within the CNS are diverse. TNF-alpha is known to induce expression of MHC Class I and II expression within the CNS, enhance viral replication and is toxic in glial cultures.88,98 In addition, TNF and other cytokines may alter the permeability of the blood-brain barrier (BBB) as observed in other CNS inflammatory diseases.99-101 Early reports suggested that the blood brain barrier was more permeable in patients with AIDS.102-104 To test the hypothesis that the BBB was more permeable in patients with HIVD compared to HIV seropositive and seronegative patients, a study of age and autopsied-time matched seronegative, preAIDS, and AIDS patients with and without HIVD was performed.98 BBB integrity was analysed by the extrusion of serum proteins into the brain parenchyma. The results of this study indicated that increased BBB permeability occurred in all patients with HIVD but rarely in AIDS patients without HIVD or seronegative controls except in those individuals with some other inflammatory neurological disease (Figure 7). Increased BBB permeability was significantly associated with diffuse myelin pallor on pathological samples and increased signal intensity in white matter of T2 weighted MRI scans in patients with HIVD. In patients with HIVD, serum proteins were detected in cortical neurons which exhibited dysmorphic appearances suggesting that these neurons were injured or dying. The mechanism underlying altered blood-brain barrier permeability is unclear although other groups have identified abnormalities in cerebral endothelia morphology in patients with HIVD.105 To examine the expression of different cell adhesion molecules on cerebral endothelia, studies of ICAM-1 and VCAM-1 were performed in the same group of patients studied in the BBB permeability analysis. These molecules were chosen because they are known to be induced by cytokines such as TNF-alpha, and bind monocytes; thus they may facilitate the CNS entry of potentially HIV-infected macrophages/monocytes.106 Detection of ICAM-1 on cerebral endothelium by immunocytochemistry was significantly greater in AIDS patients compared to seronegative controls although there were no differences between demented and

### Table: Comparison of amino acids at positions 305 and 329 for brain-derived HIV envelope clones

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<thead>
<tr>
<th>GROUP</th>
<th>POSITION 305</th>
<th>POSITION 329</th>
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<tr>
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<tr>
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Database is from “Human Retroviruses and AIDS 1993”, ed. G. Myers et al. The frequency of each amino acid at each position in the HIVD and ND groups was compared individually to the sum of all other amino acid frequencies in separate 2x2 contingency tables with Fishers Exact Test. The following P values were observed: His 305 (P < .0001), Pro 305 (P < .0001), Leu 329 (P = .0078), and Ile 329 (P = .0187). Boxed values are significantly different between HIVD and ND groups.

### Figure 5: Comparison of amino acids at positions 305 and 329 for brain-derived HIV envelope clones (reprinted by permission).

### Figure 6: Levels of TNF-alpha mRNA in the brains of AIDS patients are correlated with the clinical development and severity of HIVD (reprinted by permission).
nondemented AIDS patients. Surprisingly, VCAM-1 was identified primarily on cells within microglial nodules in patients with AIDS and rarely on cerebral endothelia. These studies suggest that the expression of certain cell adhesion molecules is enhanced in the CNS of AIDS patients which may be an initial step in the perturbation of the blood brain barrier's permeability although other groups of adhesion molecules such as the cadherins may also be involved. It is clear that immunological factors participate in the development of HIV related CNS disease with significant consequences. However, many questions remain to be answered including the specific mechanism by which different immune molecules cause neurological injury, the extent and mechanisms of immune surveillance of HIV infected cells within the CNS.

Animal Models

The use of animal models in testing many of the hypotheses presented above has become increasingly important. A variety of models have become popularized over the past decade. SIV infection of macaques and FIV infection of cats, both of which are lentiviruses, produce clinical and pathological neurologic disease. Severe combined immune deficient mice (SCID) infected intracranially with HIV display pathological features similar to HIV encephalitis. Transgenic mice have also been used to study the effects of expression of different HIV genes within the CNS. Of particular interest is the transgenic model in which HIV gp120 expressed under the control of a GFAP promoter. In this model, neuronal changes similar to those seen in AIDS patients have been observed although behavioral correlations have not yet been published.

Future Questions

HIV-related neurological disease has attracted interest from the time of the onset of the pandemic because of its high prevalence among patients with AIDS and the ensuing clues to the development of other neurological diseases. Much of the attention has been directed towards studying the clinical phenomenology and possible pathogenic mechanisms to establish a rational approach to therapy. However, important clinical issues yet to be addressed include the role of drug (AZT) resistance in CNS disease progression, epidemiological analysis of HIV-1 and HIV-2-related neurological diseases in other geographic regions affected by HIV, i.e., Africa and Asia, identification of more specific risk factors and diagnostic tools, and the development and testing of new therapies. Large steps have been made in understanding the pathogenesis of HIVD especially in the areas of immunology and neurotoxicity but a comprehensive understanding is still lacking especially in the area of pediatric HIV-associated neurological disease, likely because of the multiple mechanisms are involved. Many questions remain unanswered concerning the role of CNS viral load in relation to clinical disease, specific mechanisms underlying viral protein- and cytokine-mediated neurologic disease, the existence of other CNS receptors for HIV, host resistance genes, and complementary viruses involved in the pathogenesis of CNS disease as have been observed in animal retroviral diseases. A combined approach in the future using in vitro assays correlated with clinical findings, animal models and clinical-pathological studies will provide more insights into the pathogenesis of HIVD and the sound development of new treatments for HIVD. Further, studies of a rapidly mutating pathogen such as HIV in relation to CNS disease may permit a broader understanding of the rules governing neurovirulence that could be applied to the treatment of other CNS viruses such as HTLV-1, Japanese B and Herpes simplex encephalitides.
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REFERENCES


65. Szurlee PF, Floyd E, Yuen PH, Wong PKY. Site-directed mutagenesis of the codon for Ile-25 in gPr80™ alters the neurovirulence of Ml, a mutant of Moloney murine leukemia virus TB. J Virol 1990; 64: 5241-5429.


