Pathology of HIV-1 Infection of the Central Nervous System.  
A review.  
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Key Words: Acquired immunodeficiency syndrome; Central nervous system; HIV-1.

INTRODUCTION

This brief review will outline the historical development of the neuropathology of human immunodeficiency virus type 1 (HIV-1) infection, with reference to clinical correlates. A description follows of the various pathological findings, with a separate discussion of vascular myelopathy. Some of the newer aspects of HIV-1-associated changes in the central nervous system (CNS) will also be covered, as well selected current theories of pathogenesis. This article is not intended to be comprehensive, since several recent reviews have covered the neuropathology of HIV-1 in detail (1–5). Clinical terminology in this paper is that recommended by the AIDS Task Force Working Group of the American Academy of Neurology (6), with pathological terminology from the Consensus Report published in Brain Pathology (4).

EARLY HISTORY

The term “history” implies something that happened in the distant past; but events surrounding the acquired immunodeficiency syndrome (AIDS) began to occur just over ten years ago. At that time, in 1981, the first reports appeared describing unexplained immunodeficiency in homosexual men in the United States (7–10). It was soon apparent that many people with this syndrome had neurological dysfunction (11, 12), and in 1983 the first comprehensive report of clinical and neuropathological findings was published (13). Fifty patients were presented in that report, with neuropathological descriptions in 20 of them. Numerous papers detailing the various neurological findings followed, summarized by Michaels et al (14). The early clinical reports tended to focus on the numerous opportunistic infections that were prevalent in the CNS of AIDS patients, but there were also suggestions of a new type of encephalopathy in these people, initially attributed to cytomegalovirus (CMV) (15). Clinically, the patients manifested cognitive changes, lethargy, social withdrawal and psychomotor retardation, with marked dementia in the late stages of the illness. Soon afterward it became apparent that children could also suffer from AIDS (15, 16), and they too had an apparently new form of progressive encephalopathy (17–20).

Important discoveries in 1983 and 1984 led to recognition of a previously unknown retrovirus as the probable cause of AIDS (21–23). This virus, now called HIV-1, was ultimately classified as a member of the lentivirus subgroup of retroviruses (24). Neurologists had known for a long time that lentiviruses cause neurological disease in animals, including visna in sheep (25) and caprine arthritis-encephalitis virus (CAEV) (26). This knowledge, together with the increasing clinical recognition of what was then termed AIDS encephalopathy, fueled efforts to determine if HIV-1 itself could be responsible for the encephalopathy (19). The first published report of a link between HIV-1 and encephalopathy was the description of transmission of the virus to chimpanzees from brain tissue of adults and children who had died of AIDS with encephalopathy (27). This report was rapidly followed by identification of HIV-1 nucleic acid sequences, by in situ and Southern blot hybridization in the brains of AIDS patients (28) and shortly thereafter by isolation of HIV-1 from brain and cerebrospinal fluid (CSF) (29, 30).

As a result of the high fatality rate of AIDS, pathologists began to accumulate abundant autopsy tissue for study. Again, initial published reports stressed the many, severe opportunistic infections, in both the systemic organs (31) and the CNS (32). Changes that today are considered to be characteristic of HIV-1 infection of the CNS were slow to be recognized. The paper of Snider et al (13) described myelin pallor and disseminated glial-microglial nodules, but the hallmark of HIV-1 infection of the CNS, the infected multinucleated giant cell (MGC) (33, 34), was mentioned only in passing. Likewise, Moskowitz et al (32) described both myelin pallor, which they ascribed to CMV, and MGC, which they also did not illustrate, suggesting that these cells might be related to opportunistic measles virus infection of the brain. The first illustration of MGC in the brain of a patient with AIDS was published without comment by Horoupian et al (35) in 1984 (their Figure 2E), while the first suggestion that these cells might be related to HIV-1 was made in 1985 (33). Within one year the MGC was recognized as a marker for the AIDS virus.
other lentiviruses, MGC do not occur in vivo with visna and CAEV, but they are characteristic in both CNS parenchyma and leptomeninges of macaque monkeys infected with simian immunodeficiency virus (SIV) (50–53), the best animal model for HIV-1 infection discovered to date.

In some instances MGC have cell processes, suggesting either that they have arisen from fusion of microglial cells (54) or that they have incorporated process-bearing microglial cells within them (55). On frozen sections of brain tissue, the entire MGC cytoplasm is uniformly stained for the HIV-1 core (gag) antigen p25 by immunocytochemistry (56), although on formalin fixed, paraffin embedded sections the immunocytochemical staining may be more granular (57 and unpublished observations). Multinucleated giant cells are now considered to be essential for the diagnosis of HIV-1 infection of the CNS, in the absence of immunocytochemical or molecular biological evidence of virus (4).

The other features of HIV-1 encephalitis have been well described and illustrated in the recent neuropathology Consensus Report (4). They include loose collections of microglial and glial cells, similar to classical microglial nodules but less tightly cellular (1, 39), and white matter pallor, which is usually diffuse (HIV leukoencephalopathy) (4, 58). The latter change may be seen either with or without MGC, and it is usually accompanied by a pronounced astrogliosis, emphasized by techniques that highlight astrocytic cells such as immunocytochemistry for glial fibrillary acidic protein (GFAP). The white matter at times may also have a diffuse or focal vacuolation (vacuolar leukoencephalopathy) (4). Axons tend to be relatively spared in HIV leukoencephalopathy (1), but there can be focal axonal loss associated with focal lesions of white matter pallor (59).

The histopathological changes of HIV-1 encephalitis and white matter pallor were first convincingly related to the clinical encephalopathy by Navia and co-workers from Cornell Medical Center and Memorial-Sloan Kettering in New York (60, 61), who called the neurological syndrome the AIDS dementia complex, now termed the HIV-1-associated cognitive/motor complex (6). More recent data from Rosenblum at Memorial Sloan-Kettering (1) has strengthened the positive correlation of these findings with the degree of neurological dysfunction, although the correlation is far from complete (also, see below). The encephalitic findings (MGC and the glial-microglial collections) can be found in any part of the CNS, from the cerebral cortex to the spinal cord, but they are most readily identified in the deep white matter of the cerebral hemispheres, the basal ganglia, and the brainstem. In the white matter and basal ganglia these cellular infiltrates are often located adjacent to blood vessels, and the MGC in these regions may contain brown pigment that stains variably for iron (61).
Adult patients with the HIV-1-associated cognitive/motor complex usually have clinical evidence of atrophy of the brain upon neuroimaging (62). Although some cases may have severe atrophy (63), average brain weights have been reported to be normal, possibly related to terminal brain swelling superimposed on atrophy (61). In children, there is also clinical evidence of either brain atrophy or, in young children, acquired microcephaly (64). At autopsy, brain weights in children with HIV-1 infection are strikingly reduced compared to normal standards (65), and there is often gross atrophy as well (39).

Our own autopsy studies of CNS findings in children with HIV-1 infection have documented a constellation of histopathological changes, with MGC in 61% (22 of 36) of cases (66). In this series of 36 children (66), most of whom had HIV-1-associated progressive encephalopathy (6), white matter pathology (pallor and/or astrocytosis) was present in 78%, with glial-microglial cell infiltrates in 75%. The most frequent finding, in 92% of cases, was of vascular or juxtavascular, basophilic mineralizations (39, 67, 68) located either in the basal ganglia (putamen and globus pallidus, but not caudate), the frontal lobe white matter, or both. Approximately 30% of the brains in this series had inflammation of parenchymal blood vessel walls, also termed “cerebral vasculitides” (4). The latter two findings are more common and more prominent in the brains of children with HIV-1 infection than in adult brains (69). All studies of children with HIV-1 infection have reported a low incidence of recognizable opportunistic infections in the CNS (39, 65, 66, 70). The infrequent occurrence of troublesome opportunists in the brains of these children permitted in part the development of some of the early hypotheses concerning the role of HIV-1 in the pathogenesis of the encephalopathy (71).

HIV-1 INFECTION OF CELLS WITHIN THE CNS

A major effort among neuropathologists and other investigators studying HIV-1 infection has been to identify the cells of the CNS that are infected by the virus. Early on it was recognized that MGC and macrophages contained the virus (37). Microglial cells also were found to be infected, on the basis of in situ hybridization and immunocytochemical studies (35, 72, 73). Several groups have reported infection of endothelial cells as well (37, 57, 74, 75), but this has not been confirmed by others (47, 59, 76, 77).

With regard to neuroectodermal cells, we reported tentative identification of virus particles in the cytoplasm of a cell that contained prominent intermediate filaments, suggesting it was an astrocyte (36). More convincing was the better preserved ultrastructure of Mirra and del Rio (78), who demonstrated budding of viral particles from the plasma membrane of an astrocyte, suggesting that HIV-1 had integrated into the DNA of this cell. Most studies have failed to find localization of either HIV-1 antigen or specific nucleic acid sequences in GFAP-positive cells (73, 76, 79). However, low level, non-productive infection has been achieved in astrocyte cell lines in vitro (80).

Immunocytochemical studies purported to demonstrate infection of white matter oligodendrocytes by virus (81), but double labeling was not done. An ultrastructural study also reported the presence of HIV-1 particles in oligodendrocytes (82), but the identity of these cells was challenged by others (78, 83, 84). In retrospect, both of these studies almost certainly demonstrated HIV-1 infection in microglial cells. Scattered reports have also suggested infection of neurons by HIV-1 (75, 85, 86), but these too remain unconfirmed.

Most investigators now favor the idea that the only cells in the CNS that can be readily demonstrated to contain HIV-1 are monocyte-derived cells: macrophages, microglial cells, and MGC. As Estes (48) has noted, HIV-1 encephalitis is unique among viral infections of the CNS in that it appears to infect only these monocyte-derived cell types and no other cells.

VACUOLAR MYELOPATHY

A digression is in order to describe the clinicopathological entity known as vacuolar myelopathy. This disorder was first described in a single patient by Goldstick et al (87), who noted a resemblance to the spinal cord pathology of subacute combined degeneration. Shortly thereafter, Petito et al (88) described the clinical and pathological features of 20 patients, none of whom was there clinical evidence of vitamin B12 deficiency. Patients who are symptomatic have spasticity and leg weakness, with paraplegia in severe cases. Neuropathological examination of the spinal cord has disclosed striking spongiform or vacuolar change in the lateral and dorsal columns, without regard to tracts in the former. The presence of macrophages within the vacuoles is required for the diagnosis, in order to eliminate the possibility of artifact (88, 89). Ultrastructural studies have demonstrated intramyelinic splitting (88), although at least one investigator has reported that the vacuoles form between the axon and the myelin sheath (90). Remyelination has been described (91), and swelling of axis cylinders may occur in severe cases (56, 90).

This disorder has proven to be surprisingly controversial, with regard to both incidence and etiology. Although the entity has been reported in HIV-1 infected patients from many centers, the incidence has varied greatly, from no cases among HIV-1 infected subjects examined postmortem (92) to 55% of cases (90). The average incidence of the disorder in most autopsy series has been 20 to 30% of cases (93). This variation in incidence can perhaps in
part be accounted for by the types of patients seen at different centers, with a higher incidence expected in cases referred primarily because of neurological deterioration. In addition, diagnostic criteria may vary between neuropahtologists, although published papers do not suggest that this is the main reason for the great differences in incidence. There is, however, general agreement that this lesion is rare in children with HIV-1 infection, with only two documented pediatric cases known to this author (56).

A more heated controversy relates to the role of HIV-1 in the etiology of vascular myelopathy. Some investigators have noted a correspondence between HIV-1 type inflammatory changes and the vacuoles (94, 95). In addition, one group has demonstrated a constant association of vascular lesions with the presence of specific HIV-1 nucleic acid sequences by in situ hybridization (96). However, other investigators have not found an association between HIV-1 and the vacuoles (97, 98). While the majority of cases of vascular myelopathy occur in patients who have HIV-1 encephalitis (that is, HIV-1 type inflammatory changes in the brain) (99), this relationship is also inconstant. In addition, Kamin and Petito (89, 100) have described a similar vascular myelopathy in several patients who did not have HIV-1 infection. Some of their subjects had encephalitis or encephalomyelitis, in some cases due to CMV, suggesting that viral infection of the CNS in general might predispose to spinal cord white matter vacuolation. However, they pointed out that the most common clinical setting in their patients was underlying immunodeficiency, in some cases due to therapy for such disorders as systemic lupus erythematosus or lymphoma. The authors concluded that vascular myelopathy might be due to an as yet unidentified opportunistic infection of the CNS (89). This hypothesis might help to explain why the disorder is so rare in children with HIV-1 infection, who, as mentioned above, have a low incidence of CNS opportunistic infections in general.

RECENT DEVELOPMENTS

Recent interest from several centers has focused on documentation of pathology in the cerebral cortex in people with the HIV-1-associated cognitive/motor complex. From time to time there have been reports of severe cortical nerve cell loss associated with profound encephalopathy, in both adults and children with HIV-1 infection (39, 63, 101, 102). Some of these cases have had evidence of abundant HIV-1 infection in the devastated cortex by molecular, immunocytochemical and ultrastructural techniques. The case of Gray et al (63) is of particular interest, since the brain demonstrated much less HIV-1 involvement than the other cases and particularly because there was minimal white matter pathology, despite a typical clinical history of severe HIV-1-associated dementia complex.

Budka (103) was the first observer to point out that certain cases of HIV-1 infection had evidence of widespread astrogliosis of the cerebral cortex, which he termed diffuse poliodystrophy. More recently Ciardi et al (104) and Eskin (105) have documented similar findings. Even more important are studies from three separate groups that, using different techniques, have documented statistically significant nerve cell loss in the cerebral cortex in the brains of patients with HIV-1 infection, compared with the brains of normal control subjects (106-108). Wiley and his co-workers (108) also demonstrated a loss of synaptic density in the cortex, using immunocytochemistry for synaptophysin, and this group has presented preliminary evidence of decreased dendritic branching in AIDS brains versus controls by use of the Golgi impregnation technique (109). These studies, and others that are sure to follow, will likely focus new, deserved attention on changes in the cerebral cortex in people with HIV-1 infection.

Since 1987 the antiretroviral agent zidovudine (ZDV), also known as azidothymidine (AZT) or Retrovir, has been available for use in the treatment of people with HIV-1 infection. Early reports documented mild amelioration of the HIV-1-associated cognitive/motor complex in adult patients treated with ZDV (110, 111), and it was later suggested that the introduction of ZDV therapy had resulted in a decreased incidence of HIV-1 infected patients who presented with neurological impairment (112). More dramatic changes related to ZDV therapy were reported in HIV-1 infected children, with near normalization of the neurological examination and neuroimaging findings in some children (113-115). There is also preliminary clinical evidence that other antiretroviral agents, including dideoxyinosine (ddI) (116), have similar clinical effects. Recently, preliminary evidence has been presented from two centers on the declining incidence of neuropathological changes of HIV-1 encephalitis (117) and HIV-1-related leukoencephalopathy (118) in ZDV-treated adult patients coming to autopsy. These developments present a clear challenge to the neuropathology profession to document any CNS changes that might be attributed to these and other agents used for the treatment of HIV-1 infection (93).

PROBLEMS AND PATHOGENESIS

The greatest difficulty with current theories of the pathogenesis of the HIV-1-associated cognitive/motor complex, HIV-1-associated dementia and HIV-1-associated progressive encephalopathy of childhood is understanding the exact mechanism whereby these clinical situations arise. Much effort and thought have been devoted to this problem during the short time that the neurological picture has been recognized. However, it is not surprising that the situation is not understood, since, after
all, the exact pathogenesis of most dementing illnesses, including Alzheimer's disease, is also unknown.

Among the many questions that are currently unanswered, the chief one is why some people with typical HIV-1-associated dementia have no neuropathological evidence of HIV-1 encephalitis (1, 5, 61). One might ask what is the exact relationship, if any, of HIV-1 encephalitis to the dementia. Clinically, dementia occurs most commonly when the patient has full blown immunodeficiency or AIDS (73, 119), although there have been a few reports of patients who either presented with dementia or were demented when they were seemingly in an early stage of immunological impairment (120). A substantial proportion of adults with the HIV-1-associated dementia complex have neither encephalitic changes nor evidence of HIV-1 in the CNS (1), although children who die with severe HIV-1-associated progressive encephalopathy almost invariably have both (unpublished observations). In addition, there have been reports of patients with a heavy viral burden in the CNS but few neuropathological changes (28, 39).

HIV-1 appears to enter the CSF compartment (14), and possibly the brain compartment as well (121), early in the course of HIV-1 infection; and the majority of symptomatic and asymptomatic people have evidence of CSF infection (14). Autopsy on an asymptomatic man with HIV-1 infection who died of trauma revealed only mild chronic meningitis and cerebral white matter astrocytosis (122). Another report described autopsy findings in a man who had early, mild neurological symptoms at the time of his death. In this case there was generalized pellor of the central white matter, again with astrocytosis, as well as a small area of organizing encephalomalacia in white matter of one of the frontal lobes (123). In neither of these "early" cases was there evidence of HIV-1 encephalitis. Esiri and co-workers (124) examined the brains of a group of HIV-1 infected hemophiliacs, most of whom were asymptomatic for the virus but had died of their bleeding disorder. Esiri noted that the early cases had more perivascular lymphocytic cells in the CNS, without typical HIV-1-associated changes, leading her to postulate that the as yet unimpair ed immune response had helped to suppress viral expression within the CNS, thereby delaying the onset of both the dementia and the encephalitis (49, 124). Others have proposed that HIV-1 becomes more "neuroadapted" over the course of the infection in an individual patient, by becoming more tropic for cells of monocyte/macrophage origin with time (125). Both of these hypotheses suggest that the histopathological changes of HIV-1 encephalitis may be "late" manifestations of the disease.

If HIV-1 is responsible for the dementia, it must exert its effects either directly or indirectly, or perhaps by a combination of direct and indirect effects. Direct effects would include infection of neuroectodermally-derived cells, that is, nerve cells and glial cells. Convincing evidence for direct infection of these cell types has yet to be presented. If they are indeed infected, the number of viral copies per cell must be less than currently can be detected by even the most sensitive means, including specific nucleic acid sequence determination by in situ hybridization. Much clinical information has been presented to support the notion that the HIV-1-associated cognitive/motor complex is a subcortical dementia, in part because of the predominance of subcortical (white matter, basal ganglia) pathology (14, 73). The concept of dementia without cerebral cortical involvement is problematic, and evidence of infection of cortical neurons would greatly aid our understanding of the disorder. The recent interest in neocortical pathology in HIV-1 infected people is important and enlightening, although none of the studies has yet been able to determine whether the effects are directly or indirectly related to the virus. Infection of oligodendrocytes, if it were to occur, would help to explain the prominent white matter changes. In the absence of evidence of infection of neurons and oligodendrocytes, we must ask how infection of monocytes, macrophages, MGC and microglial cells can cause the clinical disease. Diffuse infection of the entire resident or resting microglial cell population might have a devastating effect on CNS function (126). Diffuse microglial infection has in fact been reported on the basis of immunocytochemistry (55, 72, 79), but this observation has been uncommon. Budka (5) and Kure et al (47) have noted HIV-1-positive microglial processes adjacent to neurons, suggesting the possibility of cell-cell interaction between the infected microglia and the uninfected nerve cells.

Products of HIV-1 might have an effect on CNS function, without direct infection of neuroectodermal cells themselves. The HIV-1 envelope glycoprotein gp120 has been a favorite candidate for this type of effect. A currently attractive hypothesis concerns toxic effects of gp120 on nerve cells in vitro, related to increases in intracellular calcium. These effects can be prevented by calcium channel blockers, and it has been proposed that these pharmacologic agents be used to treat the HIV-1-associated cognitive/motor complex (127). In producing these toxic effects, gp120 appears to act in concert with low concentrations of glutamate, via the N-methyl-D-aspartate (NMDA) receptor, a subclass of glutamate-binding membrane proteins. The toxic effects can be blocked by NMDA antagonists as well (see Lipton [128] for discussion).

Other investigators have suggested indirect effects related to toxic substances secreted by HIV-1 infected macrophages. Two such substances, apparently different from each other, have recently been observed in vitro experiments (129, 130). It has been suggested that various cytokines have a mediating role in the pathogenesis of the dementia. Tumor necrosis factor alpha (TNFα), which

has been found to be toxic to oligodendrocytes and myelin in vitro (131), has been reported by some observers to be secreted by HIV-1 infected macrophages (132), and a similar substance has been isolated from stimulated astrocyes (133). Some evidence has been presented to suggest that increased systemic TNFα correlates with more severe HIV-1-associated encephalopathy (134), but an increase in local TNFα production within the CNS has yet to be demonstrated.

If we have learned one lesson about infectious diseases in the last quarter of the twentieth century, it is that we do not have all the answers. Even before the AIDS epidemic was recognized, major new diseases related to infection were reported in the United States for the first time, including Legionnaires’ disease, toxic-shock syndrome, and Lyme borreliosis. Although unlikely, it is nevertheless not unreasonable to propose that the HIV-1-associated cognitive/motor complex and related neurologic disorders might be due to an as yet unrecognized, possibly opportunistic, pathogen, either old or new. It is clear that HIV-1 is present in the CNS, and this fact is obviously very important. However, the presence of the virus and the inflammatory reaction to it could be epiphenomena. From time to time various agents have been proposed to be related to the dementia, including CMV (135) and a Mycoplasma species (136); but there is currently no compelling reason to believe that an infectious agent other than HIV-1 is responsible for the neurological effects.

The first decade of the AIDS epidemic brought remarkable developments in a short period of time, including characterization of the clinical disease, discovery of its cause, and the beginning of attempts to treat it. The beginning of the second decade finds many questions still unanswered, but the rapid pace of the previous ten years suggests that we may be on the threshold of significant discoveries that will have relevance to several fields of endeavor, including the neurosciences.

ACKNOWLEDGMENTS

Dr. Leon G. Epstein and Dr. Eun-Sook Cho reviewed the manuscript and offered helpful comments. Gratitude is expressed to the many neuropathologists, named and unnamed, who have selflessly contributed to the understanding of the neuropathology of HIV-1 in the CNS, despite the potential risk to personal health that this work involves.

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