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HIV Infection of Human Choroid Plexus: A Possible Mechanism of Viral Entry into the CNS

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Abstract. The present study examines the hypothesis that HIV infection of the choroid plexus (CPx) may be an important site of viral entry into the brain. Formalin-fixed, paraffin-embedded CPx was obtained from 25 patients with AIDS and 13 nonAIDS patients and was processed for light microscopy and for immunohistochemical detection of HIV gp41, T and B lymphocytes, monocytes/macrophages and endothelial cells. Eleven of the 13 nonAIDS CPx were normal and 2 contained inflammatory foci of undetermined etiology. The stroma contained T lymphocytes in all and monocytes in 22%; B lymphocytes and HIV antigen were absent. Choroid plexus of the AIDS cases contained opportunistic infections or lymphoma in 12 and inflammatory foci alone in 6; 7 were normal. T lymphocytes were present in 70% and monocytes in 50%. In addition to the stromal localization, monocytes also were present in supra-epithelial regions and within or adjacent to the capillary endothelium. HIV-positive cells in the CPx were found in 11 cases (44%) and in the supra-epithelial area in another 2. Their presence correlated with neither infection nor lymphoma of the CPx or brain. They were situated in the stroma, supra-epithelial region and (rarely) capillary endothelium. Immunohistochemistry on serial sections identified the HIV-infected cells as monocytes, including those by capillary endothelium and in supra-epithelial areas. The study demonstrates that the CPx contains HIV-infected monocytes in almost half of the cases. Their apposition to endothelium suggests hematogenous origin. These results support the hypothesis that HIV encephalitis may develop from CPx infection.

Key Words: AIDS; Brain; Choroid plexus; Encephalitis; HIV.

INTRODUCTION

Encephalitis due to human immunodeficiency virus (HIV) is common in patients with the acquired immunodeficiency syndrome (AIDS) (reviewed in 1, 2). Its autopsy incidence is roughly 30% (3) although the actual incidence may be higher if techniques more sensitive than routine microscopic examination are employed. The virus enters the CNS during the initial stage of systemic infection. Intrathecal synthesis of HIV-1-specific antibodies (4, 5) and direct viral isolation from the cerebrospinal fluid (CSF) (6) are found in neurologically asymptomatic individuals at the time of, or subsequent to, seroconversion. It is not known whether the CSF infection is a prerequisite for the subsequent development of HIV encephalitis or whether a second hematogenous dissemination occurs at later time periods.

The mechanisms whereby HIV-1 gains access to the nervous system are not entirely understood. Most studies support the infected monocyte origin of HIV encephalitis since the HIV strains isolated from the CNS are monocytotropic rather than lymphotrophic (7–9) and since simian immunodeficiency virus (SIV) encephalitis requires inoculation by monotropic rather than lymphotrophic strains (10, 11). Direct endothelial infection by HIV is rare *in vivo* although it does occur *in vitro* (see 12, 13 for review) and may be important with animal retroviruses (12, 14, 15).

In the following study, we explore an alternative mechanism for HIV entry into the CNS; namely, that the virus gains access to the brain via passage through the choroid plexus (CPx). The rationale for this hypothesis is threefold. First, CPx capillaries are outside the blood–brain barrier (BBB) (16) and thus may permit ready passage of infected monocytes or lymphocytes into the CPx stroma. Second, the CPx has been implicated as the site of entry for other infectious agents (17–20). Third, HIV-1 can latently infect a subpopulation of cells isolated from the human CPx (21). Accordingly, we collected postmortem CPx from patients with AIDS and nonAIDS controls and examined them for the presence of HIV antigens, inflammation, and infection. Immunohistochemistry was used to identify HIV gp41 glycoprotein, T and B lymphocytes, and monocytes/macrophages. A preliminary report has been published (22).

MATERIALS AND METHODS

Archival formalin-fixed CPx of 25 AIDS patients and 13 nonAIDS control patients was used for this study. The AIDS cases were randomly selected from stored brains from which CPx was available whereas the controls were selected to specifically exclude any with brain infections, HIV infection, AIDS or immunosuppression, as reported in the autopsy records. The material was embedded in paraffin, cut at 7 μm and deparaffinized sections were stained with hematoxylin-eosin (H&E) and prepared for immunohistochemistry to identify HIV, T and B lymphocytes, endothelial cells and monocytes/macrophages.

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Monoclonal antibodies employed included HIV gp41 (1:750 to 1:1,200 dilution) from Genetics Systems, Inc., Seattle, WA. The remainder were obtained from Dako Corp., Carpinteria, CA, and included: T cells (CD45Ro; 1:125 to 1:400 dilution); B cells (CD45R; 1:75 dilution); macrophages (CD68; 1:125 to 1:200 dilution with trypsin predigestion for 1 hour [h]); and endothelium (Factor VIII; 1:750 and CD41; 1:40). Following blocking with normal serum and overnight incubation with the primary antibody, sections were washed and sequentially incubated with biotinylated secondary antibody and the avidin-biotin complex (Vector Labs, Burlingame, CA). Chromogens included hydrogen peroxide with 3'3'-diaminobenzidine (brown), VIP (purple) or alkaline phosphatase-anti-alkaline phosphatase (red). A light counterstain with hematoxylin was then added. Positive controls included tonsil, CNS lymphoma and HIV encephalitis. The primary antibody was omitted from the diluent for a negative control. In addition, the identification of intravascular monocytes and T and B lymphocytes in most cases confirmed the validity of the results. Alternative markers for T and B lymphocytes (CD3 and CD20) and for monocyte/macrophage markers (*Ricinus communis* agglutinin I and HAM 56) were unsatisfactory since background was too high or since endothelium and CPx epithelium showed nonspecific staining. The number of inflammatory cells or HIV-positive cells were difficult to quantitate since their distribution was usually non-uniform. We used a semiquantitative non-parametric scale as follows: mild = <5 cells per 10 high power fields (HPF); severe = ≥1 cell per 2 HPF; and moderate = remaining cases.

The cell type infected by HIV was identified by single-label immunohistochemistry on serial sections and by double-label immunohistochemistry, using a slight modification of the procedure of Kure et al (23) for the double-labeling. We tried varying the dilutions and the order of the primary and secondary antibodies as well as the primary and secondary chromogens. The biotinylated secondary antibody was horse anti-mouse IgG for the first primary antibody and goat anti-mouse IgG for the second primary antibody. Two additional AIDS cases with numerous HIV-positive cells in the CPx and otherwise normal brains also were used since sufficient material was not always available in the cases initially selected for this report.

RESULTS

The average age of the 25 AIDS patients was 40.8 years (yr) (range 29 to 61 yr); 24 were male and 1 was female. Risk factors for HIV infection included homosexuality in 9, intravenous drug abuse (IVDA) in 4, bisexuality in 1, homosexuality plus IVDA in 1, sexual promiscuity in 1 and unknown or unacknowledged in 9. The mean postmortem interval was 32 h (range 7–82 h). Neuropathological changes in the brains included the following: HIV encephalitis - 12; lymphoma - 7; CMV - 6; toxoplasmosis - 5; cryptococcus - 4. Fifteen of these had more than one CNS disease and 6 had more than one opportunistic infection (OI) or lymphoma. Twelve had vacuolar myelopathy and 1 had HIV myelitis (data not shown). Four had normal brains exclusive of CPx pathology, but all of these had systemic infections (Table 1).

The average age of the 13 nonAIDS controls was 47 yr (range 0.7–83 yr); 4 were male and 9 were female. None were known to be infected by or at risk for HIV. The mean postmortem interval was 34 h (range 16–79 h). One case had a chronic ventriculitis of undetermined etiology that was characterized by focal ependymal cell loss and subependymal gliosis. The CNS of the remainder were either normal (n = 3) or had unrelated brain diseases (n = 9). None had CNS infection, although 7 of the 13 had evidence of systemic infection at the time of death (Table 1).

The CPx in 12 of the AIDS cases had OI (n = 6), lymphoma (n = 5) and OI plus lymphoma (n = 1). Ten of these had the same lesion in the brain although there was no association between CPx HIV and HIV encephalitis (see below). The CPx was usually normal in the nonAIDS cases. Focal inflammation of uncertain etiology was encountered in only 2. Both patients were women in their fourth or fifth decades, one of whom had septic shock and the other of whom had multiple brain infarcts due to systemic atherosclerotic cardiovascular disease.

Immunolabeling in the 9 nonAIDS cases with available material detected T lymphocytes in all (Fig. 1A) and monocytes in 2 (Fig. 1B); extravascular B lymphocytes and HIV antigen were always absent. In the AIDS cases, T lymphocytes were present in 69.5% and monocytes in 52%; extravascular B lymphocytes were absent in all cases. In both groups of patients, the T lymphocytes and monocytes were found within the stroma or in close proximity to blood vessels. Monocytes were also present in a supra-epithelial location in several of the AIDS cases.

Eleven of the 25 AIDS cases (44%) had HIV immunoreactive cells in the CPx stroma (Fig. 2A). Associated changes in these CPx included lymphoma in 5 and OI in 2; the remaining 4 were normal. The HIV-positive cells were few in number in 6 cases (nos. 1–4, 6, 7) but were numerous and diffusely distributed throughout the CPx in the remaining 5. They were present within the endothelium of the stromal capillaries in 2 cases (Fig. 2B). Two additional cases (nos. 12 and 13) contained HIV-positive cells in the adjacent CSF (Fig. 2B). These were designated as "supra-epithelial" cells since we could not be certain whether they were true epiplexus monocytes or CSF monocytes entrapped in the tissue at the time of fixation.

Double-label immunohistochemistry showed co-labeling of HIV and monocyte immunoreactivity but the results were limited by nonspecific background staining. Serial sections with single-label immunohistochemistry avoided the background staining but itself was limited by the absence of the same cell in adjacent sections. However, when the same HIV-positive cell was present on the adjacent serial section prepared for cell-specific markers, it labeled with the monocyte marker, including the HIV-

TABLE 1
Neuropathology of Choroid Plexus and Brain

No.	Choroid plexus infections and lymphoma	Choroid plexus inflammation		Brain pathology
		T cell	Monocyte	
AIDS patients				
1	HIV; CMV	+	O	CMV; toxoplasmosis
2	HIV; cryptococcus	+	+	HIVE; cryptococcus; Wernicke's
3	HIV; lymphoma	++	O	lymphoma
4	HIV; lymphoma	O	O	HIVE; lymphoma
5	HIV; lymphoma	O	O	lymphoma
6	HIV	+++	+++	O
7	HIV	+++	+++	HIVE; atypical lymphocyte infiltrate
8	HIV	+++	+	focal necrosis
9	HIV	+++	+++	O
10	HIV	+	O	HIVE; CMV
11	HIV	+++	+++	HIVE
12	HIV (supra-epithelial)	+	+	HIVE; focal necrosis
13	HIV (supra-epithelial)	+	+	basal ganglia atrophy
14	toxoplasmosis	+++	na	CMV; toxoplasmosis
15	candida	na	na	HIVE; cryptococcus
16	candida	O	O	O
17	cryptococcus	O	O	HIVE; cryptococcus; toxoplasmosis
18	CMV; lymphoma	O	+++	CMV; lymphoma
19	lymphoma	+++	O	lymphoma; toxoplasmosis
20	lymphoma	+	O	lymphoma; toxoplasmosis
21	O	+++	+++	HIVE; lymphoma
22	O	++	na	HIVE; CMV
23	O	O	+	O
24	O	na	na	HIVE; CMV
25	O	O	O	HIVE; cryptococcus
NonAIDS patients				
1	O	+++	O	multiple infarcts
2	O	+++	O	Alzheimer type II astrocytes
3	O	++	+++	Alzheimer type II astrocytes
4	O	+++	O	metastatic carcinomatosis
5	O	+	O	chronic ventriculitis
6	O	+	O	ruptured saccular aneurysm
7	O	++	O	normal brain
8	O	+++	O	normal brain
9	O	na	na	multiple infarcts
10	O	na	na	normal brain
11	O	na	na	normal brain
12	O	na	na	multiple infarcts
13	O	+	++	focal brain stem atrophy

Abbreviations: CMV: cytomegalovirus; HIVE: HIV encephalitis; na: not available.

positive cells within or adjacent to capillary endothelium (Fig. 2C, D) and in the overlying CSF (Fig. 2C–G).

DISCUSSION

The anatomic characteristics of the CPx (16, 24) render it particularly vulnerable to systemic infections or to deposition of macromolecular substances such as amyloid, hemosiderin and immune complexes. Its capillaries have gap junctions (16) rather than the tight junctions of the intraparenchymal capillaries (25). Thus, the CPx lies outside the BBB and there is ready passage of macromolecules from the blood stream into its stroma. However, there is a blood–CSF barrier which is formed by a combination of tight junctions between the CPx epithelial cells (16) as well as by an absence of transcellular passage through the epithelium of substances from the stroma into the CSF (26).

The CPx is a normal component of the neuroimmune system. Cell adhesion molecules (intercellular and vascular adhesion molecules) are expressed on its epithelium as well as on ependymal cells (27, 28). With inflammation or interferon treatment, these are upregulated and class II major histocompatibility antigens are expressed. The CPx stroma contains T lymphocytes and monocytes

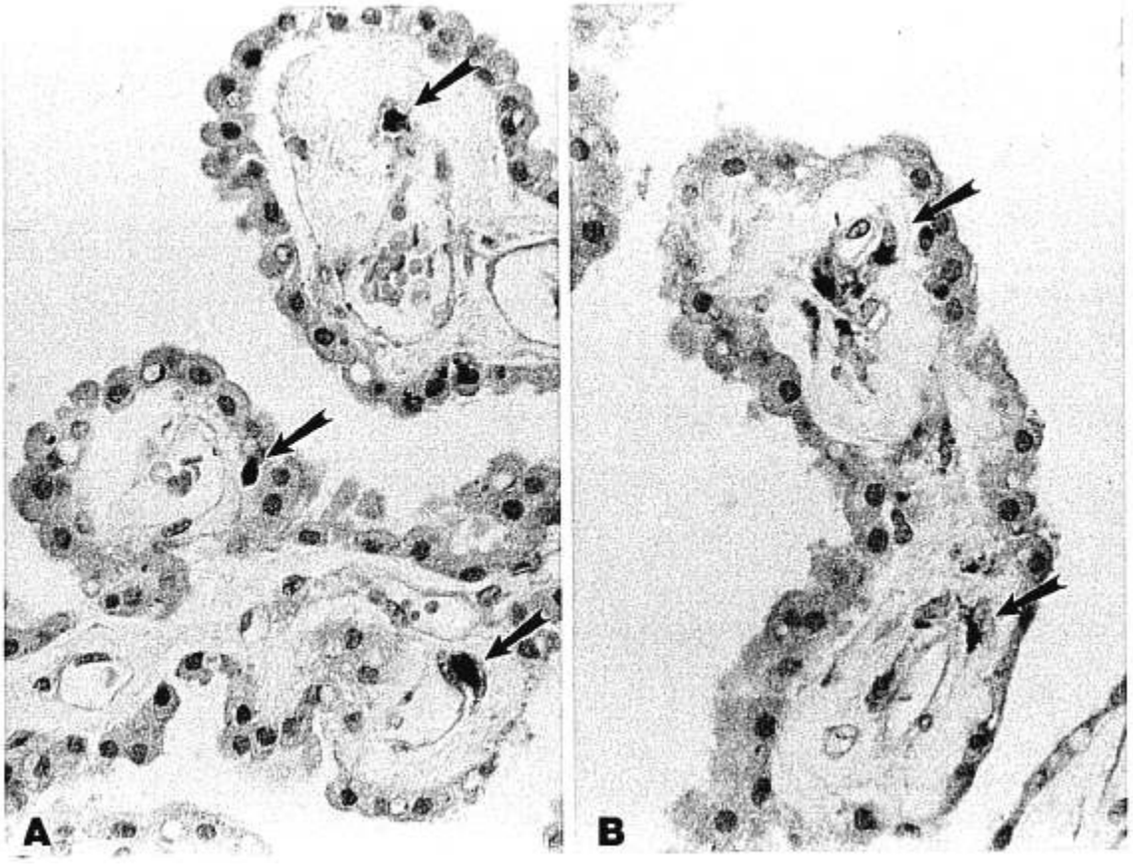

Fig. 1. Control choroid plexus. Immunostain for T lymphocytes (A) and monocytes (B) shows the distribution of these cells (arrows) in the stroma and around blood vessels in the choroid plexus. Hematoxylin, ×800.

(29–31) which Hickey et al (32) have shown to be derived from the circulation. Their ready passage into the CPx contrasts with the more restricted movement of these cells into the brain parenchyma itself (32–34). Thus, the CPx is an ideal site for infected T lymphocytes and monocytes to enter the CSF and gain ready access to brain parenchyma through the ependymal lining. Finally, the CPx may contain a population of dendritic cells similar to those of lymphoid organs and skin (unpublished data).

The present study shows that the CPx often is infected or infiltrated by HIV-positive cells. We found no evidence to suggest a "Trojan horse" mechanism (35) of infection, whereby infected monocytes would enter the CPx in response to co-existing diseases. Rather, the CPx was normal in 6 of the 11 cases with HIV infection of this structure. Although there was no apparent relationship between HIV-infected CPx and the presence of other infections or lymphoma of the CPx or the brain, the number of cases studied may not have been sufficiently large to detect such an association. Thus, we cannot entirely exclude the possibility that co-existing diseases of the CPx increase its vulnerability to HIV infection.

The absence of HIV immunoreactivity in the CPx of nonAIDS controls is an important measure of the reliability of these results since Parmentier et al (36) recently have found HIV regulatory proteins in noninfected human tissue, and since connective tissue, which is abundant in the CPx, often has nonspecific antibody binding.

Serial sections using single-label immunohistochemistry identified many HIV-positive cells as monocyte/macrophage cells, including those within or close to the capillary endothelium. We were unable to detect HIV immunoreactivity in fibroblasts, endothelial cells or epithelial cells. These results may indicate that prior demonstrations of endothelial infection may actually have identified trafficking inflammatory cells infected with HIV. However, our data is limited by the fact that the same cell often was absent on adjacent serial sections. Thus, we cannot exclude HIV infection in cells other than monocytes until additional studies, such as combined immunohistochemistry-*in situ* hybridization, are completed.

Infection of CPx by HIV may have several important consequences. First, the CPx could serve as a reservoir for HIV during the asymptomatic period of clinical latency, much in the same fashion as has been recently

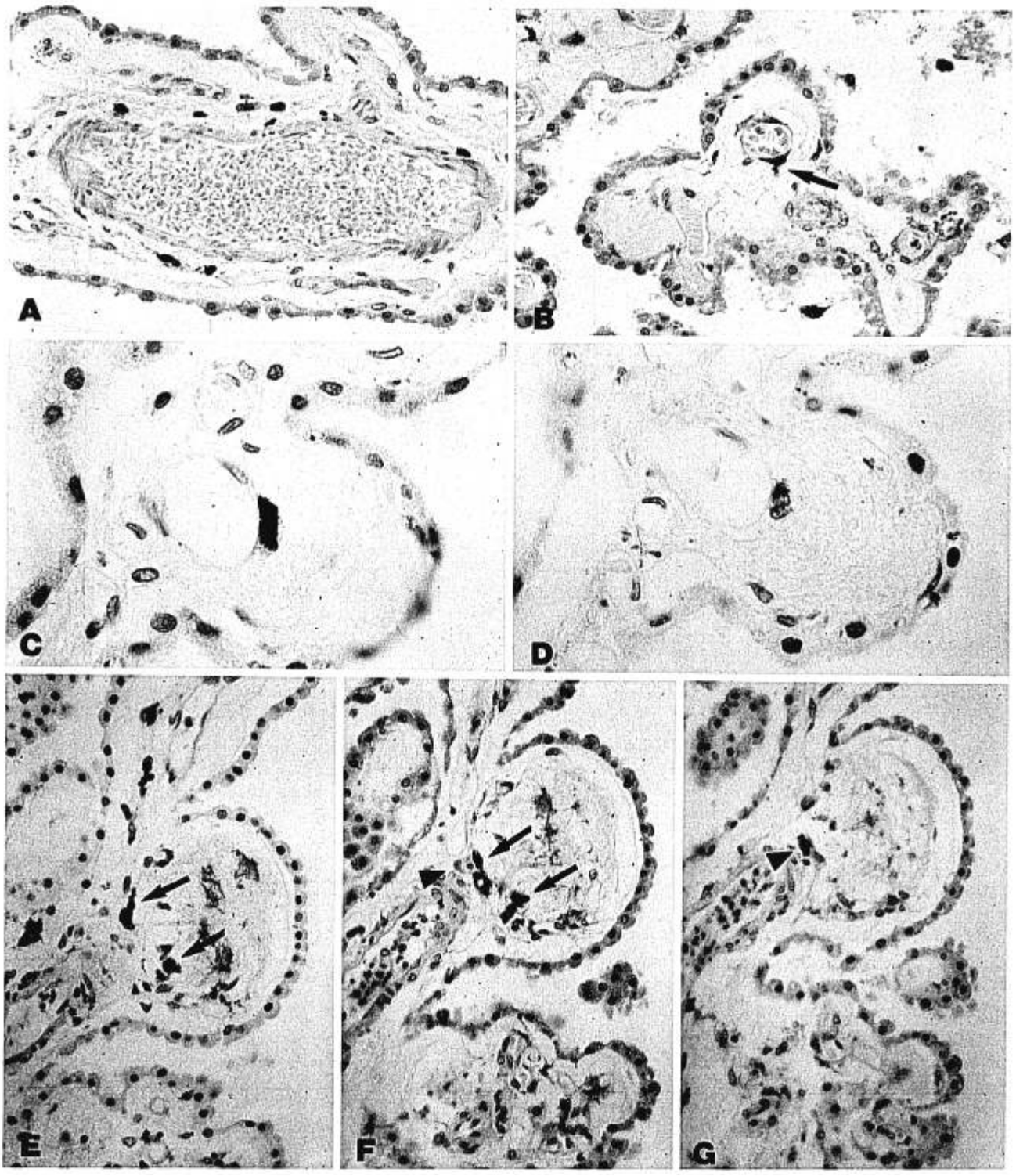

Fig. 2. AIDS choroid plexus. Immunostain for HIV gp41 (A, B, C and F), monocytes (D, E) and T lymphocytes (G). A: HIV-positive cells in CPx stroma. B: HIV-positive cells in capillary endothelium (arrow), stroma and CSF space. C and D: Serial sections showing that the HIV-positive cells in C also label with the monocyte marker CD68 in D. E, F and G: Serial sections showing that HIV-positive cells (long arrows) in F are positive for the monocyte marker in E and negative for the T lymphocyte marker in G. In contrast, the T lymphocyte (arrowhead) in G fails to stain for HIV in F. Hematoxylin counterstain. A, B, E–G ×400; C, D ×1,000.

shown to occur in dendritic cells of lymphoid organs (37–39). Alternatively, or in addition, the CPx could be an important site whereby HIV enters the brain, as originally hypothesized by Harouse et al (21).

Although initial studies suggest that leptomeningeal or perivascular monocytes are the first cells in the CNS to support productive HIV or SIV infection (40, 41), a more recent study has found that CPx, as well as perivascular cells, is the first site of infection in feline immunodeficiency virus infection (42). Other lines of evidence offer indirect support to the potential importance of the CPx as the route of HIV entry into the CNS. First, hematogenously derived monocytes are more numerous in the CPx and leptomeninges than the brain parenchyma (32). Second, CPx involvement is common in experimental retroviral infection. Simian immune deficiency virus infection of *Macaca mulatta,* the closest experimental model of HIV infection, produces CPx inflammation in 44% of animals infected with a neurotropic strain of SIV (43); meningeal inflammation occurred in 50% and encephalitis in 55%. Another study found not only inflammation and multinucleated giant cells but also SIV antigens and RNA in the CPx of SIV-infected animals (44). Visna, another retroviral infection associated with CNS disease, also is accompanied by CPx infection as an early and common feature of its neuropathological lesions (45). Finally, the CPx is an important or sole site of initial hematogenous dissemination of other CNS infections including retroviruses as described above (43–45), parasites (17, 19, 20), and bacterial and fungal (18, 46, 47) diseases. Experimental studies showing that this structure is the initial site of hematogenous dissemination in African trypanosomiasis (17, 19) support the hypothesis that the CPx is important in the development of brain infections.

The presence of HIV-infected monocytes rather than HIV-infected T lymphocytes in the CPx is relevant to the development of subsequent HIV encephalitis. In macaques infected with a lymphotrophic strain of SIV, infected lymphocytes readily traffic into and can be cultured from the CSF during the initial post-inoculation period. However, they do not give rise to SIV encephalitis (10). Rather, encephalitis arises only when animals are inoculated with a monocytotropic variant of SIV which is highly neurovirulent and which specifically infects brain microglia (11).

A parallel situation may occur in HIV infection although the present study did not specifically address this hypothesis since viral tropism was not examined and since HIV-infected, asymptomatic cases were not available. Lymphocytes infected with HIV could enter via CNS vessels and move in and out of the CSF and the extracellular spaces of the brain. Since activated lymphocytes normally traffic into the CNS (33, 34), their presence in the brain parenchyma of HIV-infected patients would be expected. HIV encephalitis would not occur until the development of AIDS and specific monocytotropic variants of HIV. Indeed, gene amplification studies show that HIV DNA is rare or absent in the brains of asymptomatic HIV-infected patients (40, 48). At this point, the CPx could play an important role in the pathogenesis of HIV encephalitis by permitting entry of HIV-infected monocytes from blood to CPx to CSF from whence they could enter and infect microglia in periventricular or subpial brain parenchyma. Although a BBB leak is common in AIDS patients, it is not specific to HIV encephalitis (49, 50) and is not accompanied by inflammatory infiltrate (49).

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