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The Shifting Patterns of HIV Encephalitis Neuropathology

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HIV infected macrophages infiltrate the nervous system early in the progression of HIV infection, leading to a complex set of neuropathological alterations including HIV encephalitis (HIVE), leukoencephalopathy and vacuolar myelopathy. This in turn results in neurodegeneration of selective cellular populations and pathways involved in regulating cognitive and motor functioning. Rapid progress in the development of highly active antiretroviral therapy (HAART) has changed the patterns of HIV related neuropathology and neurological manifestations in the past 10 years. The prevalence of opportunistic infections and central nervous system (CNS) neoplasms has decreased, and some groups have proposed that the frequency of chronic forms of HIVE have been rising as the HAART-treated HIV population ages. Accordingly, clinical manifestations have shifted from severe dementia forms to more subtle minor cognitive impairment, leading to the suggestion of a classification of HIV associated neurological conditions into an inactive form, a chronic variety, and a 'transformed' variant. From a neuropathological point of view these variants might correspond to: a) aggressive forms with severe HIVE and white matter injury, b) extensive perivascular lymphocytic infiltration, c) 'burnt-out' forms of HIVE and d) aging-associated amyloid accumulation with Alzheimer's-like neuropathology. Factors contributing to the emergence of these variants of HIVE include the development of viral resistance, immune reconstitution, anti-retroviral drug toxicity and co-morbid factors (*e.g.*, methamphetamine, HCV). More detailed characterization of these proposed variants of HIVE is important in order to better understand the pathogenesis of HIV-associated neurological damage and to design more effective treatments to protect the nervous system.

Keywords: HIV; Encephalitis; HAART; Chronic; Opportunistic infections; HCV; Methamphetamine; White matter; Amyloid

INTRODUCTION

Worldwide, the HIV epidemic continues to be one of the most serious public health problems facing humanity in the 21st century. Although most cases concentrate in sub-Saharan Africa, India and Asia, it is estimated that over 1 to 1.5 million individuals in the US and Western Europe are living with HIV. Since the early days of the pandemic, both clinical and pathological studies uncovered the remarkable fact that not only was the immune system vulnerable to HIV, but the nervous system was also affected in over 75% of the cases (Grant *et al*., 1988; Grant and Heaton, 1990). These patients developed acute and subacute neurological syndromes that are usually associated with CNS involvement by opportunistic infections or lymphoid neoplasms. In contrast, a subacute or chronic presentation with diffuse neurological symptoms and cognitive/movement impairment is most likely associated with direct CNS involvement of HIV. It is widely recognized that HIV penetrates the CNS via transmigration of infected monocytes/macrophages that in turn trigger a series of neuroinflammatory responses culminating in HIVE (Gendelman *et al*., 1997; Wu *et al*., 2000; Cosenza *et al*., 2002; Fischer-Smith *et al*., 2004; Kramer-Hammerle *et al*., 2005). With the introduction of highly active antiretroviral (HAART) agents and more effective antimicrobial treatments, the involvement of the CNS by neoplasms and opportu-

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nistic infections has decreased (Jellinger *et al*., 2000; Masliah *et al*., 2000; Langford T *et al*., 2002a; Bell, 2004). Initially, some of these studies also suggested that the abundance of HIV in the brain and the severity of HIVE have declined with the use of HAART (Price, 1994; McArthur *et al*., 2003). However, as the number of treated subjects with chronic HIV infection increases, the prevalence of HIV-associated cognitive and neurological impairment is actually rising despite treatment with HAART (Maschke *et al*., 2000; Sacktor *et al*., 2002; Gray *et al*., 2003; McArthur *et al*., 2003). It is now becoming apparent that these patients may be suffering from protracted forms of HIVE (Gray *et al*., 2003; Bell, 2004) that might lead to more subtle cognitive alterations rather than to overt dementia (Cherner *et al*., 2002; Diesing *et al*., 2002; Lawrence and Major, 2002; Gonzalez-Scarano and Martin-Garcia, 2005). Thus, HIVE might have shifted from a subacute rapidly progressive condition to a chronic neurodegenerative process since patients are living longer with HIV and the brain is an important reservoir for this virus (Dougherty *et al*., 2002; Gray *et al*., 2003; Cysique *et al*., 2004; McArthur, 2004; Cook *et al*., 2005). It was proposed that clinically, these patients might progress to an inactive form, a chronic variety, or a 'transformed' variant (Lawrence and Major, 2002). Understanding the mechanisms by which HIV leads initially to cognitive dysfunction and eventually to dementia is important for development of new treatments for this devastating condition.

CHANGING PATTERNS IN THE NEUROPATHOLOGY OF AIDS

Established in 1991, the classification of HIV-related neuropathology remains useful in the present (Budka, 1991). It is accepted that HIVE is characterized by the presence of HIV infected cells in the brain, accompanied by the formation of multi-nucleated giant cells (MNGC, FIG. 1A), microglial nodules (MGN, FIG. 1B, 1C), microgliosis (FIG. 1D), astrogliosis (FIG. 1E), and myelin pallor (FIG. 1F, 1G) (Budka, 1991; Achim *et al*., 1992; 1993; Wiley and Achim, 1994; Bell *et al*., 1998; Langford T *et al*., 2002b). The macrophage/microglial cell is the primary target of HIV in the CNS (FIG. 1H) (Wiley *et al*., 1986; Cosenza *et al*., 2002; Fischer-Smith *et al*., 2004), however low levels of the provirus have been detected in other cell populations including astrocytes, endothelial cells and neurons (Bagasra *et al*., 1996; Takahashi *et al*., 1996; Torres-Munoz *et al*., 2001; Mukhtar *et al*., 2002; Trillo-Pazos *et al*., 2003). After the microglia, the astroglial cells appear to be significantly affected by HIV-1. Astrocytes are the most affected in the CNS of pediatric AIDS cases, where these cells express high levels of the HIV protein, Nef (Anderson *et al*., 2003). Several postmortem studies published recently compared and reviewed the changing patterns of the pathology of AIDS in the pre- and post-antiretroviral therapy era (Jellinger *et al*., 2000; Masliah *et al*., 2000; Neuenburg *et al*., 2002; Gray *et al*., 2003). Opportunistic infections and non-Hodgkin primary lymphomas of the CNS remain late complications that appear in untreated or poorly adherent patients. Among these, cytomegalovirus (CMV), toxoplasma, and lymphoma can diffusely involve the CNS or have a periventricular distribution (Mamidi *et al*., 2002). Progressive multifocal leukoencephalopathy, caused by the JC virus, initiates at the grey/white matter junction causing destruction of the myelin (Bell, 2004). Most of these opportunistic infections diminished in frequency in the HAART era. However, the increasing prevalence of other infections, such as hepatitis B and C (HCV), appear to exacerbate HIV disease (Chung *et al*., 2001). The role of HCV associated with intravenous drug use is of interest in the changing patterns of HIV neuropathology. In addition to the astroglial activation in the basal ganglia (Alzheimer's type 2 glia) associated with hepatic failure, HCV might co-infect and traffic with HIV in macrophages into the CNS (Laskus *et al*., 2000; 2004; Radkowski *et al*., 2002; Vargas *et al*., 2002; Forton *et al*., 2004a,b).

The mechanisms leading to cognitive impairment and dementia in AIDS patients are not completely understood. However, most recent studies suggest that when HIV-infected monocytes/macrophages traffic across the blood-brain barrier (BBB), they in turn activate other neuro-inflammatory cells such as microglia and astrocytes (Mirra and del Rio, 1989; Pulliam *et al*., 1991; Gendelman *et al*., 1994; Langford D and Masliah, 2001; Minagar *et al*., 2002; Wiley, 2003; Speth *et al*., 2005). These cells produce chemokines, cytokines and neurotoxins that, in conjunction with secreted HIV proteins, damage the synapto-dendritic arbor of neurons leading to neuronal dysfunction and eventually to neuronal cell death probably via apoptosis (Giulian *et al*., 1990; Pulliam *et al*., 1994; 1998; Meucci *et al*., 1998; Sanders *et al*., 1998; Kaul and Lipton, 1999; Martin-Garcia *et al*., 2002; Brandimarti *et al*., 2004; Wang *et al*., 2004). These observations suggest that levels of HIV in the brain might reflect the extent of the structural and functional neuropathology (Brew *et al*., 1995; Glass *et al*., 1995; McArthur *et al*., 1997).

The introduction of HAART also impacted the pat-

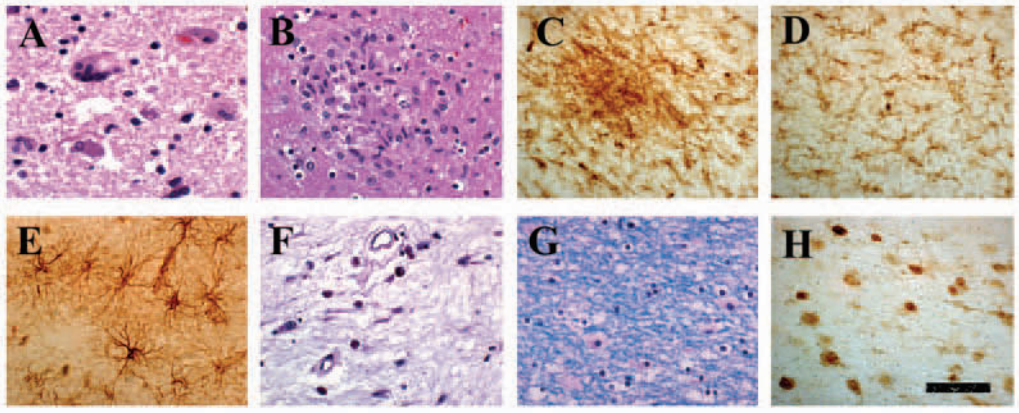

FIGURE 1 Patterns of HIVE neuropathology. (**A**) Multi-nucleated giant cells (H&E). (**B**) Microglial nodules (H&E). (**C**) Microglial nodules (anti-CD45). (**D**) Microglial proliferation (anti-CD45). (**E**) Diffuse astrocytosis (anti-GFAP). (**F**) Extensive white matter damage in an HIVE case with history of METH use (LFB). (**G**) Mild white matter rarefaction in an HIVE case (LFB). (**H**) HIV-positive macrophages in the frontal cortex (anti-p24). Scale bar 35 µm.

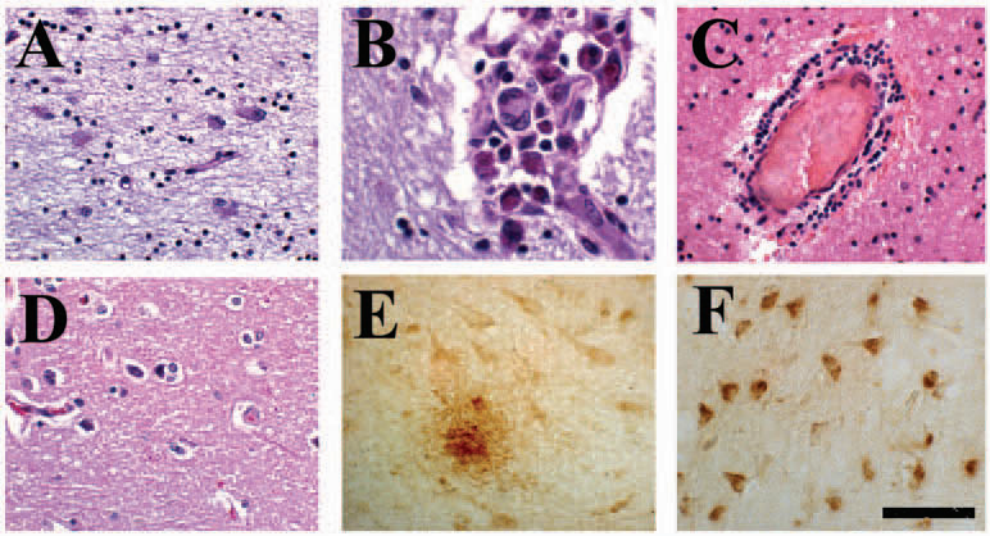

FIGURE 2 Neuropathology of the HIVE variants. (**A**) Severe white matter injury with astrogliosis (LFB). (**B**) Vascular infiltration in the white matter by macrophages (PAS). (**C**) Lymphocytic perivascular infiltration (H&E). (**D**) 'Burnt-out' form with neuronal atrophy (H&E). (**E**) Plaque-like lesions (anti-Aβ, 4G8). (**F**) Intra-neuronal Aβ (anti-Aβ, 4G8). Scale bar 35 µm.

terns in HIV-related neuropathology in the past 10 years. HAART resulted in a decline in opportunistic infections of the CNS and neoplasms, but as HAART-treated individuals survive longer and to an older age. This is accompanied by an increase in the frequency of chronic forms of HIVE (Langford T *et al*., 2002a; Gray *et al*., 2003; Cysique *et al*., 2004; Anthony *et al*., 2005; Cook *et al*., 2005). It has been proposed that emerging variants of HIV neuropathology in HAART-treated patients include: a) aggressive forms with severe HIVE and white matter injury (FIG. 2A, 2B), b) extensive perivascular lymphocytic infiltration (FIG. 2C), c) 'burnt-out' forms of HIVE (FIG. 2D) and d) β-amyloid (Aβ) accumulation with Alzheimer's-like neuropathology (FIG. 2E, F). Chronic 'burnt-out' forms of CNS infection appear to develop as a result of prolonged survival. In these cases no overt inflammation and no infectious agent are detected. Instead, focal white matter pathology, nonspecific lesions with gliosis and neuronal atrophy are found (Gray *et al*., 2003) (FIG. 2D). Since the beginning of the AIDS epidemic, several investigators recognized that HIV involvement of the CNS associates with white matter gliosis and demyelination (Budka, 1991) independent of JC virus infection. In fact, leukoencephalopathy might be one of the central manifestations of HIVE, and its association with the development of HIV neurocognitive disorders is often overlooked due to primary focus on neuronal injury. Neuroimaging studies corroborate that white matter injury continues to be a significant problem in patients with HIV (Aylward *et al*., 1995). Furthermore, it was shown that abnormalities in the

white matter may be associated with the use of neurotoxic stimulants such as methamphetamine (Thompson *et al*., 2004), cocaine and other drugs of abuse (Lyoo *et al*., 2004). In the more aggressive forms of HIVE, abundant HIV-infected macrophage/microglial cells can be found, accompanied by MNGC, vasculitis and myelin and axonal injury (Langford D *et al*., 2003). In HIV-infected individuals leukoencephalopathy may be caused by HIV-, immune-, opportunist-, or drug-associated neurotoxic mechanisms.

Diffuse damage of the white matter is detected more frequently in patients with cognitive impairment and is characterized *in vivo* by diffuse or focal hyperintensity as shown by MRI (Aylward *et al*., 1995) and by mild to moderate myelin loss and astrogliosis at autopsy (Smith *et al*., 1990; Budka, 1991). HAART may improve cognitive impairment (Sacktor *et al*., 2002), however, HIV-infected patients treated with HAART more frequently display extensive focal white matter lesions in neuroimaging studies as compared to those not taking antiretrovirals (Ammassari *et al*., 1998; 2000). The frequency of neuro-opportunistic infections has decreased with the advent of prophylactic therapies such as nucleoside reverse transcriptase inhibitors (NRTIs) and later of non-nucleoside reverse transcriptase inhibitors (nNRTIs) (Masliah *et al*., 2000). Moreover, in the initial phases of treatment after the introduction of protease inhibitors (PIs), there was a relative decrease in opportunistic infections and HIVE (Jellinger *et al*., 2000). However, a surge in the frequency of HIVE (Neuenburg *et al*., 2002) and in particular of a highly destructive form of HIV-associated leukoencephalopathy (HAL) (Langford T *et al*., 2002b) was observed probably due to the emergence of HAART-resistant forms of HIV. We recently reported seven autopsy cases of leukoencephalopathy in antiretroviral-experienced patients with AIDS and severe immunosuppression (Langford T *et al*., 2002b). All seven patients had poorly controlled HIV replication despite combination antiretroviral therapy and HIV-associated cognitive impairment. Neuropathologically, all brain samples had intense perivascular infiltration as detected by HIV-gp41 immunoreactive monocytes/macrophages and lymphocytes (FIG. 2B), widespread myelin loss (FIG. 2A), axonal injury (FIG. 2A), microgliosis and astrogliosis. The extent of damage seen in these cases exceeded that described prior to the use of HAART. Furthermore, brain tissue demonstrated high levels of HIV RNA, but no evidence of other viral pathogens. In this pattern, white matter damage begins with perivascular infiltration by HIV-infected monocytes and lymphocytes, which may occur as a consequence of antiretroviral-associated immune restoration. Massive infiltration by immune cells injures brain endothelial cells followed by myelin loss, axonal damage, and finally, astrogliosis (FIG. 2A-2C).

In addition to these more severe forms of white matter damage, during the HAART era, focal white matter lesions without mass effect or contrast enhancement have become a frequent observation (Ammassari *et al*., 2000; Gray *et al*., 2003). HIV itself could injure white matter by infecting or damaging oligodendrocytes or brain endothelial cells or by directly damaging myelin via myelinotoxic viral proteins, such as gp120 or Tat (Arese *et al*., 2001). These observations are consistent with reports of an increased incidence of focal white matter lesions in HAART-treated patients (Ammassari *et al*., 2000) and of an unexpectedly high incidence of "not determined" leukoencephalopathy in AIDS patients (Antinori *et al*., 2000). Compared with the white matter injury that occurred prior to the use of HAART, the leukoencephalopathy we describe differs primarily in its severity. In the past, perivascular infiltration by mononuclear cells and myelin loss was less extensive, white matter atrophy was milder, and HIV levels in the brain were lower (Smith *et al*., 1990). In comparison, our cases are characterized by massive perivascular macrophage infiltration, extensive demyelination, and evidence of very high levels of HIV replication in the brain.

Factors potentially contributing to the emergence of these variants of HIVE include aging, the development of viral resistance, immune reconstitution, anti-retroviral drug toxicity and co-morbid factors such as methamphetamine use and HCV co-infection. Of particular interest are those forms associated with white matter damage (Gray *et al*., 2001; Langford T *et al*., 2002a; Lawrence and Major, 2002; Bell, 2004). A rather remarkable recent observation in HIV-infected patients over 50 years of age is the presence of abundant intracellular Aβ-immunoreactive aggregates accompanied by occasional diffuse plaques (FIG. 2E, 2F), reminiscent of Alzheimer's disease, however no extensive neuritic and neurofibrilary pathology is observed (Green *et al*., 2005; Rempel and Pulliam, 2005). Consistent with these observations, the incidence of minor cognitive/motor impairment increased, while overt dementia has become less frequent.

PATTERNS OF NEURONAL INJURY IN AIDS PATIENTS

In addition to white matter damage, the neurodegenerative process in HIV infection is characterized by den-

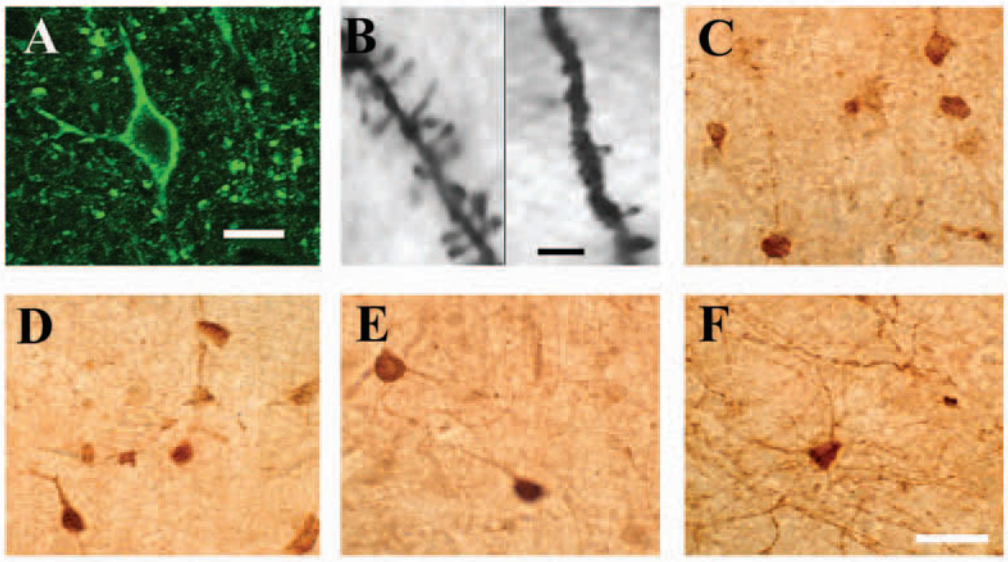

FIGURE 3 Patterns of neuronal damage in HIVE. (**A**) Dendritic damage and neuronal atrophy in the frontal cortex (anti-MAP2). (**B**) Loss of spines in apical spines in HIVE (panel to the right) compared to an age matched control (panel to the left) (Golgi impregnation). (**C**) Damage to calbindin-immunoreactive interneurons in HIVE (anti-CB). (**D**) Damage to interneurons in HIVE+methamphetamine (anti-CB). (**E, F**) Damage to parvalbumin-immunoreactive interneurons in the neocortex and hippocampus (anti-PV). Note that the density of interneurons is decreased and their neuritic process are diminished. Scale bar for A= 15 μm, for B= 2 μm and for C-F= 25 μm.

dritic simplification of pyramidal neurons and selective loss of interneurons (FIG. 3) (Budka, 1991; Masliah *et al*., 1994; 1996b). Furthermore, there is damage to the microvasculature resulting in BBB compromise (Dallasta *et al*., 1999; Langford D and Masliah, 2001). The neurodegenerative process affects primarily the striato-cortical, cortico-cortical, and limbic intrinsic/inhibitory circuitries (Masliah *et al*., 1996a). It is not known if these circuitries are affected simultaneously or if there is a temporal progression of the neurodegenerative process from one site to another. The neuronal populations most severely affected in these regions include large pyramidal neurons in the neocortex (FIG. 3A) (Budka *et al*., 1987; Everall *et al*., 1991; Wiley *et al*., 1991a; Masliah *et al*., 1992c; Weis *et al*., 1993; Fox *et al*., 1997), spiny neurons in the putamen (Masliah *et al*., 1992b; 1996b), medium-sized neurons in the globus pallidus, and interneurons in the hippocampus (Masliah *et al*., 1992b; 1995; Fox *et al*., 1997). In the frontal, parietal, and temporal cortices of HIVE cases, there was a 30-50% decrease in large neurons, accompanied by a 20% reduction in neocortical width (Gray *et al*., 1991; Wiley *et al*., 1991a; Everall *et al*., 1992; 1994; 1997; Maslia *et al*., 1992a; Weis *et al*., 1993; Asare *et al*., 1996). Using image analysis techniques, a statistically significant 30-50% decrease in the number of large neurons (200 to 500 μm^2) was identified in the frontal, parietal, and temporal cortices of HIVE cases; this damage was accompanied by a reduction in neocortical width (up to 20%) and astrocytosis. These changes were described as diffuse poliodystrophy (Budka, 1991). Consistent with neuropathological studies, analyses of the brains of AIDS patients and observations in animal models show similar alterations in neuronal markers such as *N*-acetyl-aspartate by nuclear magnetic resonance (NMR) spectroscopy (Wilkinson *et al*., 1997; Marcus *et al*., 1998; Gonzalez *et al*., 2000).

Studies in experimental animal models as well as observations in the brains of AIDS patients indicate that neuronal damage may start in synapses and dendrites (FIG. 3A-3C) and then spread to the rest of the neuron, thereby activating pathways leading to cell death via apoptosis (Fox *et al*., 1997; Everall *et al*., 1999; Garden *et al*., 2002). Supporting this possibility, studies in the brains of HIVE patients show evidence of DNA fragmentation in neurons, glia and endothelial cells, as determined by the TUNEL assay (Adle-Biassette *et al*., 1995; Everall *et al*., 1997; Wiley *et al*., 2000; Gray *et al*., 2001). Moreover, there is caspase-3 activation as well as pro-apoptotic gene expression (James *et al*., 1999; Garden *et al*., 2002). The mechanisms involved in neuronal and synaptic degeneration in AIDS patients are complex, but most evidence supports the contention that infected and or activated microglia/macrophages release toxic factors such as viral products, excitotoxins, and/or cytokines and chemokines that in turn damage neurons by multiple mechanisms (Gendelman *et al*., 1994; Kaul *et al*., 2001). These factors may also stimulate production of chemokines and cytokines by astrocytes that affect neuronal functioning (Pulliam

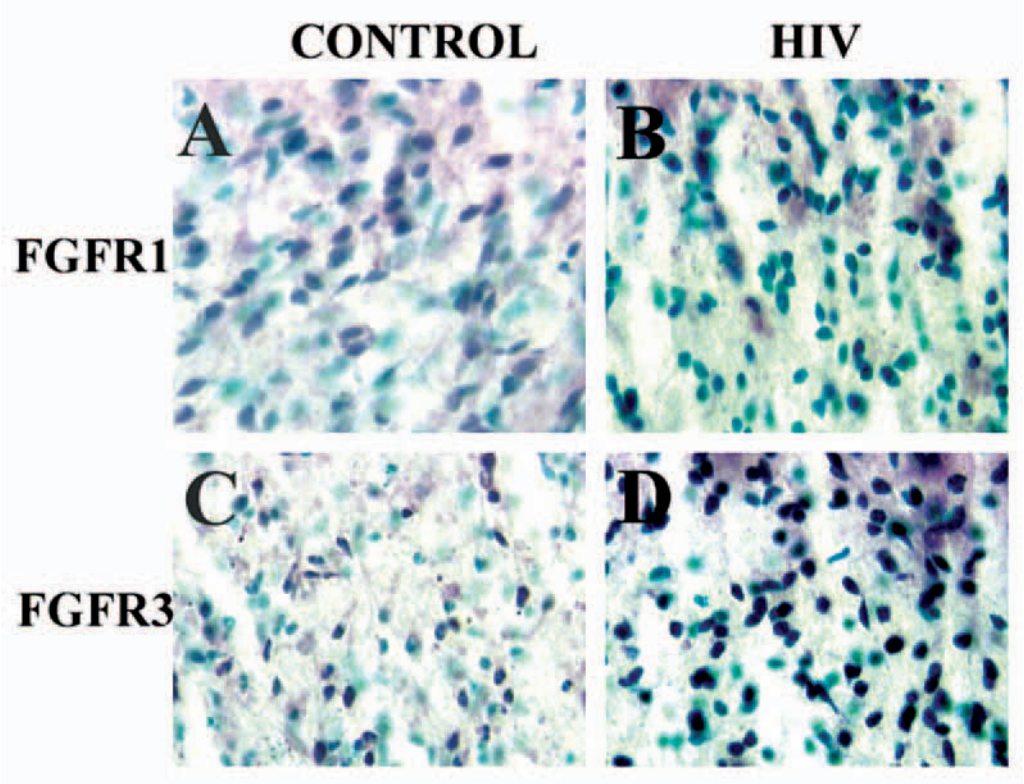

FIGURE 4 FGFR expression in primary human nervous system cultures infected with HIV. (**A**) Anti-FGFR1 immunostaining in uninfected control sample. (**B**) FGFR1 immunoreactivity in an HIV-infected sample. (**C**) Anti-FGFR3 immunostaining in uninfected control sample. (**D**) FGFR3 immunoreactivity in an HIV-infected sample.

et al., 1991; Benveniste, 1994; Minagar *et al*., 2002). During the progression of HIVE, different neurotoxic factors are released and it is likely that a diverse range of neuronal populations are affected in the most vulnerable areas of the CNS, including the frontal cortex, basal ganglia, hippocampus and white matter.

In the limbic system of patients with HIVE, pyramidal neurons are relatively spared, however, there is a significant loss of parvalbumin (PV)-immunoreactive interneurons (FIG. 3F) in the CA3 region (Masliah *et al*., 1992b; 1994; 1996b), which contains neurons that express cytokine receptors for interleukin 1β (IL-1β), IL-6, and tumor necrosis factor-α (TNFα). Dysfunction of the dopaminergic system has also been implicated to play a critical role in the clinical manifestation of HIV-associated dementia (HAD) (Lopez *et al*., 1999; Nath *et al*., 2000; Zauli *et al*., 2000). Moreover, in the basal ganglia of patients with HIVE, there is significant loss of large spiny neurons that express MAP-2 and contain glutamate receptors (Martin *et al*., 1993); however, neurons that express the calcium-binding protein calbindin (CB) are relatively spared (Masliah *et al*., 1996b). Somatostatin-immunoreactive neurons contain glutamate receptors and may therefore be susceptible to HIV-mediated damage (Fox *et al*., 1997; Ramirez *et al*., 2001). Somatostatin immunoreactivity in the interneurons of the frontal cortex, hippocampal pyramidal and non-pyramidal cells, and globus pallidus is significantly reduced in HIVE.

In the neocortex, pyramidal cells express microtubule associated protein 2 (MAP2, FIG. 3A), neurofilament, glutamate and cytokine/chemokine receptors and low levels of calcium-binding proteins, and interneurons have high expression levels of both cytokine/chemokine receptors and calcium-binding proteins (FIG. 3C) (Masliah *et al*., 1992b; 1994, 1995; 1996b). Interestingly, in patients with HIVE and a history of methamphetamine use, CB-expressing interneurons are specifically vulnerable to injury (FIG. 3D) (Langford D *et al*., 2003). These cells display extensive fragmentation and disruption of their neuritic processes, and in early stages aberrant sprouting and disorganization has been observed. Recent *in vitro* studies suggest that synergistic effects of HIV proteins such as tat and stimulant drugs such as methamphetamine mediate neuronal damage via mitochondrial alterations, oxidative stress and changes in calcium homeostasis (Langford D *et al*., 2004).

Differences in the relative levels of glutamate receptors, growth factor receptors, chemokine/cytokine receptors and calcium binding proteins such as CB and PV in different neuronal populations may determine their selective vulnerability to distinct HIV-induced

neurotoxins during the course of HIVE (Masliah, 1996). Neurons vulnerable to HIV toxicity express high levels of chemokine receptors such as CXCR4 and low levels of trophic factor receptors such as fibroblast growth factor receptor (FGFR) (Sanders *et al*., 2000). We have recently assessed the expression of FGFR1 (FIG. 4A, 4B) and 3 (FIG. 4C, 4D) in human brain aggregates exposed to HIV-1 sf162 overnight as previously described (Kandanearatchi *et al*., 2002). Stereological estimations of the density of cells expressing FGFR1 revealed a 50% reduction in HIV-1 sf162-exposed aggregates, 26 (SD 11) FGFR1 immunopositive cells per mm^3 in the control group compared to 13 (4) in the HIV-1 sf162-exposed group (Student's *t* test on log transformed data, $t = 4.429$, $p = 0.0001$). However, the expression of FGFR3 remained unchanged. These preliminary data indicate that alteration in the expression of receptors for trophic factors such as FGF may determine the response to HIV and possibly lead to neuro-cognitive impairment.

It is anticipated that the HAART could transform the subacute neuroinflammatory condition seen in HIVE into a chronic more subtle process (Langford *et al*., 2002a; Gonzalez-Scarano and Martin-Garcia, 2005), and neurodegeneration particularly involving synapses and dendrites will become a more prominent feature. Furthermore, due to the chronic state of HIVE, degeneration of neuronal populations usually not affected by acute HIVE might also be observed. Other factors such as toxicity triggered by HAART and the emergence of more aggressive and resistant HIV-1 strains could also play a role in the increased susceptibility of distinct neuronal populations to HIV-mediated toxic events.

HIV NEUROPATHOLOGY AND NEUROPSYCHOLOGICAL IMPAIRMENT

The relationships between HIVE, neuronal/myelin damage and dementia are complex because several viral and host-derived factors, as well as compensatory mechanisms, might play a role in this process. For example, while 70% of patients with HIVE show cognitive impairment and neurodegeneration, the remaining 30% are cognitively unimpaired and there is no evidence of neuronal injury (Glass *et al*., 1995; Masliah *et al*., 1996a; Everall *et al*., 2001; McClernon *et al*., 2001). Conversely, 35% of patients without HIVE or other significant neuropathology are cognitively impaired, while the remaining 65% are cognitively unimpaired (Buttini *et al*., 1998; Cherner *et al*., 2002).

Although HIV in the brain is most abundant in the frontal cortex, basal ganglia and white matter (Brew *et al*., 1995; Wiley *et al*., 1998), less prominent infection is present in the limbic system and brainstem (Masliah *et al*., 1996a). In the CNS, HIV predominantly infects macrophages and microglial cells and the amount of virus-infected cells correlates with the extent of neuropathological changes and severity of HIVE (Persidsky *et al*., 1999).

All patients with minor cognitive motor disorder [MCMD] or HAD and 80% of the cases with mild impairment demonstrated evidence of HIVE at autopsy (Cherner *et al*., 2002). Among patients who were neuropsychologically normal at the time of testing, 45% had mild HIVE at death. When all neuropsychologically impaired patients were grouped together, 95% of impaired subjects were found to have HIVE. In terms of diagnostic accuracy, the sensitivity of the neurocognitive diagnosis for HIVE was 67%, while the specificity was 92%. The correlation between the semiquantitative measure of brain viral burden, HIV gp41 levels, and the clinical global rating of impairment showed a modest but significant association (Spearman Rho = .39, $p < .02$).

This finding differs somewhat from previous work suggesting that brain viral burden correlates to a lesser extent to cognitive deficits (Johnson *et al*., 1996), except in cases with moderate to severe dementia (McClernon *et al*., 2001). Part of the discrepancy may stem from differences in definitions of dementia, as well as in the sensitivity of instruments or methods used to detect more subtle impairments (*e.g.*, comprehensive neuropsychological battery *vs* neurologic exam, or briefer neuropsychological assessments) (Ellis *et al*., 1997). While the presence of neuropsychological impairment appears to be a highly specific indicator of brain involvement, the absence of deficits did not indicate a corresponding absence of HIVE in every case. This suggests that the addition of other markers such as indicators of neuroinflammation and neuronal damage might increase the sensitivity of the diagnostic tests and the strength of the correlations.

However, the fact that most of the correlations between HIV levels and cognitive status were of moderate strength suggests that other factors might also contribute to and mediate the severity of the dementia. Among them, levels of macrophage infiltration and activation in the CNS and extent of the damage to the synapto-dendritic structure of neurons figure prominently (Glass *et al*., 1995; Everall *et al*., 2001; Masliah, 2001; Nukuna *et al*., 2004). Other factors that need to be taken into account in these clinico-pathological studies are the interval between clinical examination and death and antiretroviral status.

CONCLUSIONS

In view of the potential changing patterns of HAD in the era of HAART, new and more detailed studies will be needed to better understand the relationship between HIVE and dementia and to evaluate the impact of the therapies. Three types of HIV-associated pathology appear to exist in the HAART era: the inactive form, a chronic variety, and a 'transformed' variant. The potential role of other confounding factors in the development of these forms, such as the use of intravenous and stimulant drugs, anti-retroviral toxicity, viral mutations, HCV and Alzheimer's disease, are currently under investigation and will be important to consider in future studies correlating neurologic deficits with HIV in the brain.

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