The Pathogenesis of HIV-Associated Dementia: Recent Advances Using a SCID Mouse Model of HIV-Encephalitis

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ABSTRACT

In the era of highly active antiretroviral therapy (HAART) there has been a decrease in AIDS death rates and a reduction in HIV-related neurological complications. However, Human Immunodeficiency Virus-1 (HIV)-associated dementia (HAD) still affects at least 7% of HIV-positive individuals. Despite significant advances in HIV research there are still questions surrounding the pathogenesis of HAD. Clinical information and pathological studies suggest that the frontal cortex, basal ganglia, and hippocampus are important neuroanatomical areas involved in HAD. Recent studies utilizing a severe combined immunodeficiency (SCID) mouse model of HIV-encephalitis (HIVE) indicate that central nervous system (CNS) viral load determines the severity of astrogliosis, an important feature of HIVE. Human and animal studies suggest that viral strains may also be important in the pathogenesis of HAD. A recent study suggests that HAART does not eradicate virus in the brain, and therefore, the CNS is a reservoir for HIV. Future research efforts need to focus on the role of viral strain and mutations in the pathogenesis of HAD.

INTRODUCTION

Since the advent of highly active antiretroviral therapy (HAART) in 1996, Acquired Immune Deficiency Syndrome (AIDS) death rates have decreased by 50% and the incidence of HIV-associated dementia (HAD) has decreased by 40% (Brodt et al., 1997; Sacktor et al., 2001). While the rate of HAD has been decreasing, the prevalence has actually been increasing (6.6:100 in 1994 compared to 10.1:100 in 2000) (McArthur et al., 2003). Additionally, studies suggest a linear increase in the rate of HAD with increasing age (6% in ages 15-34 compared to 9% in ages 74 and up) (Antinori et al., 2004, Valcour et al., 2004). This may be due to an aging population of HIV-positive individuals who are more susceptible to neurological insults, ultimately leading to more cases of HAD. Thus, while HAART has benefited HIV patients in general, its efficacy in treating HIV infection of the brain is still questionable.

Due in part to some uncertainty as to which specific features of HAD pathology, termed HIV-encephalitis (HIVE), correlate with the clinical expression of dementia, the pathogenesis of HAD is incompletely understood (Kaul et al., 2001; Wesselingh and Thompson, 2001). In order to begin to elucidate which pathological features are associated with the demented condition, a severe combined immunodeficient (SCID) mouse model of HIVE has been developed. This review will focus on the clinical findings, pathological manifestations, and pathogenesis of HAD, as well as the use of the SCID mouse model of HIVE in studying this disease.

CLINICAL FINDINGS OF HAD

HAD constitutes approximately 5% of AIDS-defining illnesses (McArthur et al., 2003) and these patients develop a number of clinical abnormalities. Early on, bradyphrenia, or slowness, is commonly seen. Patients appear apathetic or depressed (Atkinson and Grant, 1997). In addition to bradyphrenia they have subcortical features, including memory impairment, impairment of executive functions, and mood abnormalities (Navia et al., 1986; Paul et al., 2002a). Typically, the symptoms in various dementias will suggest a region of the brain that is affected. For example, Alzheimer’s disease is a cortical dementia and is typically associated with problems with language functions (Paul et al., 2002a). However, the clinical features of HAD suggest that it is a subcortical dementia, and therefore structures beneath the cortex are being affected.

In the era of HAART, severe HAD is generally seen in HAART-naïve patients and those that have been taken off of HAART due to viral resistance. A milder form that may be chronic is now most frequently seen in some patients on HAART (Paul et al., 2002a). This disease has been given the term “mild cognitive-motor disorder”
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**FIGURE 1:** The Proposed Mechanism for Neuronal Damage during HIV Infection.

**FIGURE 2:** Representative photomicrograph of astrogliosis (anti-GFAP, Chemicon) in uninfected mice (A) and SCID/HIVE mice (B) and p24 positive cells (anti-HIV p24, DAKO) (C) at 200X magnification, using immunoperoxidase staining.
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Neuropsychological testing has allowed certain clinical features to be further defined and it is now known that there are problems with information processing, the speed of processing information, memory, and other aspects of behavior that also suggest the pathology includes subcortical structures (Hall et al., 1996; Paul et al., 2002a). These include the basal ganglia, where increased viral antigen is seen (Kure et al., 1990), and deep white matter, particularly the frontal lobe. The hippocampus, the hallmark region for memory encoding, has also been implicated. In addition, the basal ganglia, frontal lobe, and hippocampus are known to be involved through the use of brain imaging. White matter pallor, which is observed pathologically, can also be detected with magnetic resonance imaging (MRI) as white matter hyperintensities on T2 weighted images (Paul et al., 2002b). However, this feature, which is thought to be caused by increased water content in the white matter, is probably not relevant to the pathogenesis of HAD (Power et al., 1993). In addition to the use of MRI, positron emission tomography (PET) imaging has indicated that early in the progression of the disease deep gray matter structures, such as the basal ganglia, are also affected (Hinkin et al., 1995). MRI data in patients with HAD indicates a loss of volume, particularly in the deep gray matter structures and cortical atrophy (DalPan et al., 1992; Stout et al., 1998). Taken together, the clinical manifestations and brain imaging studies indicate that the frontal lobes, including cortex, basal ganglia, and hippocampus are areas that are affected in HAD.

PATHOLOGY OF HIV-1 ENCEPHALITIS

Like the clinical features stated above, the pathology of HIVE has also indicated that the frontal lobes, including cortex, basal ganglia, and hippocampus are affected (Kure et al., 1990; Everall et al., 1991; Petito et al., 2003). Common features of HIVE include infected mononuclear phagocytes (i.e. macrophages and microglia) and multinucleated giant cells (present in basal ganglia, midbrain, cerebellum and subcortical white matter), and to a lesser degree, astrocytes (Takahashi et al., 1996). Additionally, diffuse astrogliosis, microglial nodules, enlargement in the frontal horn of the lateral ventricle (Gelman, 1993) and, as previously mentioned, white matter pallor (Budka, 1991) are also pathological characteristics. In terms of inflammation, an accumulation of T cells in the hippocampus has been reportedly shown in autopsy tissue of patients that had HAD (Petito et al., 2003). There are a number of neuronal abnormalities including decreases in neuronal cell counts, reduced dendritic arborization, and neuronal apoptosis, indicating that neurons are affected (Wiley et al., 1991; Everall et al., 1991; Everall et al., 1993). However, HIV does not infect neurons. To better explain these neuronal findings, two theories have been postulated. The direct theory suggests neuronal injury is caused by neurotoxic HIV proteins that directly bind to neuronal receptors (Dreyer et al., 1990). The indirect theory suggests that the damage is caused by HIV-infected and/or activated mononuclear phagocytes and astrocytes which induce inflammatory responses, immune activation, and the production of neurotoxic factors (Lipton and Gendelman, 1995). Both theories are supported in the literature and, more than likely, both play a role in causing neuronal injury.

There are a number of immune factors that are seen in HIVE, including cytokines, such as tumor necrosis factor-α (TNF-α) and IFN-β, chemokines, like monocyte chemotactrant protein-1 (MCP-1/CCL2) (Kelder et al., 1998), and various metabolites, such as arachidonic acid (Genis et al., 1992). Immunohistochemistry in HIVE brains has demonstrated several proinflammatory cytokines, namely TNF-α, which is observed on perivascular mononuclear phagocytes and microglia, and interleukin (IL)-1, found on endothelium, perivascular cells, and microglia (Tyr et al., 1992; Zhao et al., 2001). Additionally, mRNA expression of these cytokines has been examined in the brains of HIV-infected patients, comparing demented to non-demented patients; the data showed that TNF-α is increased in demented patients (Wesselingh et al., 1993). Furthermore, the data suggest that increasing amounts of TNF-α mRNA are associated with an increase in severity of dementia (Wesselingh et al., 1993).

While the presence of HIV-infected mononuclear phagocytes, gliosis, and increased expression of TNF-α are probably consistent features of HAD and HIVE (Tyr et al., 1992; Wesselingh et al., 1993), there are other pathological aspects of HIVE that are less reliably associated with HAD. White matter pallor and the presence of multinucleated giant cells, for example, are both only seen in a relatively small percentage of HAD patients (Glass et al., 1993). Another conflicting finding is the lack of a consistent association between neuronal death and/or apoptosis and the severity of dementia (Everall et al., 1991; Asare et al., 1996; Petito and Roberts, 1995; Adle-Biassette et al., 1999). In fact, research has suggested that frank neuronal cell death is not necessarily required for the clinical expression of the disease. Studies examining HAD in the era of HAART have demonstrated a reversal of dementia in some, but not all, HAD patients who receive treatment (Tozzi et al., 1999; Sacktor et al., 1999; Ferrando et al., 1998). This indicates that neurons are still viable, but are probably physiologically dysfunctional. Perhaps even more surprising is the relationship of viral load to...
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the development of HAD. Whereas some studies have reported a direct relationship between viral load in the central nervous system (CNS) and severity of dementia (Wiley and Achim, 1994; McArthur et al, 1997; Ellis et al., 1997), others have not (Portegies et al., 1989; Johnson et al., 1996). Therefore, it has been suggested that while the presence of virus is necessary to induce neurological disease, the amount of virus present may not be important (Tyor et al.; 1995; Persidsky et al., 2001).

PATHOGENESIS OF HIV ENCEPHALITIS

Because HIV does not infect neurons, it is believed that the pathogenesis of HIVE is the result of neurotoxins produced by HIV-infected and activated cells in the CNS (Lipton and Gendelman, 1995). Once HIV crosses the blood-brain barrier (BBB), either alone or in infected cells, it can infect microglia, macrophages, and to a lesser extent, astrocytes within the brain parenchyma. This infection results in the release of HIV-proteins, cellular metabolites, cytokines, and chemokines, all of which are potentially toxic to neurons (Kaul et al., 2001; Meucci et al., 1998). In addition, uninfected macrophages and microglia become activated by the factors that are released from HIV-infected cells. Microglial activation, through autocrine and paracrine actions, can result in an increase of cytokine and chemokine production, and upregulation of adhesion molecules on other CNS cell types including astrocytes, endothelial cells, and pericytes (Lipton and Gendelman, 1995, Gartner, 2000). Also, activated microglia produce the excitatory amino acids, glutamate and cysteine, which can be neurotoxic (Giulian et al., 1990; Yeh et al., 2000).

Several HIV proteins are neurotoxic and include gp120, tat, and nef (Meucci et al., 1998; Maragos et al., 2003, Nath, 2002; Werner et al., 1991). Tat also appears to have chemokine properties, which may result in the recruitment of mononuclear phagocytes to the site of infection (Albini et al., 1998; Benelli et al., 2000). In addition to viral proteins, the cellular metabolites quinolinic acid, neopterin, arachidonic acid, glutamate, cysteine, nitric oxide and NTox have neurotoxic effects and are probably involved, to varying degrees, in HIVE (Giulian et al., 1990; Genis et al., 1992; Heyes et al., 1989; Lipton et al., 1993; Griffin et al., 1994; Yeh et al., 2000). Proinflammatory cytokines, namely TNF-α, IL-1, IFN-α and platelet activating factor (PAF) have also been implicated in the pathogenesis of HIVE. TNF-α is toxic to oligodendrocytes, alters neuronal function, and stimulates mononuclear phagocytes. By stimulating mononuclear phagocytes, TNF-α can cause an increase in the amount of neurotoxins that are produced (Tyor et al., 1995). IFN-α is elevated in the cerebral spinal fluid (CSF) of HIV-infected demented versus non-demented patients (Rho et al., 1995). Interestingly, when IFN-α has been used in treatments for diseases such as cancer, it is associated with a reversible subcortical dementia when the amount given is in sufficient quantities to be detected in the CSF. Chemokines, including Regulated upon Activation of Normal T-cell Expressed and Secreted/CCL3 (RANTES) and MCP-1, also appear to be elevated in HAD (Kelder et al., 1998). Increased chemokine production may result in activation and attraction of circulating and/or resident CNS cells that could further contribute to the production of neurotoxins.

Recently it has been suggested that certain strains of HIV may be more neurovirulent than other strains. For instance, it has been demonstrated that certain sequence variations of the HIV env gene are found in HAD patients compared to nondemented AIDS patients (Ranga et al., 2004; Power et al., 1994). Strains of HIV are loosely categorized according to their co-receptor preference. In order to efficiently enter a cell, HIV’s gp120, must bind to a CD4 molecule (Dalglish et al., 1984), followed by binding to a co-receptor, usually either of the chemokine receptors CXCR4 or CCR5. HIV is able to infect any cell expressing the CD4 molecule.

**FIGURE 3:** Uninfected mice learn the location of the submerged platform as determined by a significant reduction in time from day 1 to day 6, whereas SCID/HIVE mice do not.
and an appropriate co-receptor. Some of these cell types include lymphocytes, macrophages, and dendritic cells. Generally, strains of HIV that infect helper T lymphocytes are called T-tropic or X4 and use the CXCR4 as a co-receptor (Cowley, 2001; Clapham and McKnight, 2001), while strains that infect macrophages are called monocytotropic, or R5, and use the CCR5 as a co-receptor (Cowley, 2001; Clapham and McKnight, 2001). Because of its propensity to infect cells of the monocytic lineage, including microglia, R5, strains are most frequently found in the brains of AIDS patients. The contribution of specific HIV viral strains to the development of HAD is unclear but is an area that deserves considerable attention.

Clearly, numerous factors have been implicated in the pathogenesis of HAD and most likely direct and indirect mechanisms of neurotoxicity are involved (Figure 1). Taken together, it is believed that the presence of HIV in the brain and the resultant cellular and immune activation leads to the production of neurotoxins. Therefore, unlike what occurs systemically during AIDS, the CNS enters a state of immune activation.

A SCID MOUSE MODEL OF HIV ENCEPHALITIS

One way by which the pathogenesis of HAD can be clarified is through the use of animal models. Several animal models of CNS retroviral disease have been developed; like all animal models, they have their advantages as well as limitations. The simian immunodeficiency virus (SIV) Macaque model and the feline immunodeficiency virus (FIV) in cats enable researchers to study the effects of these viruses both systemically and within the CNS (Lackner et al., 1991; Power et al., 1998; Sharma et al., 1992). While the viral genomes of SIV and FIV are similar to HIV and these models resemble HIV infection in humans, there are some aspects of SIV and FIV infection that are dissimilar to HIV. Initial attempts to monitor the CNS effects of wild type SIV strains resulted in little neuropathology. The development of SIV encephalitis was facilitated by deriving strains that induce more characteristic features of HIVE. There are also murine models available, some of which involve xenografts or the use of other retroviruses such as murine leukemia virus (Bazler and Zachary, 1991; Tyor et al., 1993; Persidsky et al., 1996; Potash et al., 2005). Transgenic models have recently been developed that express single HIV proteins such as gp120, tat, and the HIV-long terminal repeat (Toggas et al., 1994; Maragos et al., 2003; Corboy et al., 1992). These models allow researchers to study the effects of a single viral protein, several of which are known to be neurotoxic. However, these models may be limited if the pathogenesis of HAD is due to multiple viral genes. In addition, if there are effects specific to the entire HIV genome, transgenic and other animal retroviruses may not fully recapitulate HIVE. Nevertheless, these models have increased our understanding of viral-host interactions and the pathogenesis of CNS retroviral disease. Therefore, the use of various models will continue to provide valuable insight into CNS viral, inflammatory, and even neurodegenerative disease.

In the early 1990’s, the SCID mouse model of HIVE, a human xenograft model, was developed at Johns Hopkins University (Tyor et al., 1993). Original studies isolated human peripheral blood mononuclear cells (PBMC), which were injected intracerebrally into SCID mice because they are less likely to reject xenografts. Human cells were used because HIV does not productively infect mouse cells. Initially, HIV was injected separately from the PBMC and control mice were injected with human PBMC alone or HIV alone. These early experiments utilized several different strains of HIV, all of which infected PBMC (Tyor et al., 1993). These strains included HTLV-IIIB, predominantly an X4 strain, and HIV-1Ba-L and HIVada, predominantly R5 strains (Tyor, et al., 1993). Surprisingly, the SCID mice injected with PBMC and HIV developed pathology similar to HIVE, regardless of whether the HIV strain was X4 or R5. However, the pathological manifestations only occurred in approximately 60% of mice injected in this manner. When primary human monocytes infected with HIVada, an R5 isolate, were injected intracerebrally, HIV-induced encephalitis was more consistently produced (Persidsky et al., 1996). Generally, the human xenografts persist for four to five weeks and this model recapitulates many of the pathological and behavioral features seen in human HIVE (Tyor et al., 1993; Persidsky et al., 1996; Avgeropoulos et al., 1998; Griffin et al., 2004; Cook et al., 2005).

Brain sections of SCID/HIVE mice (mice with HIV-induced encephalitis) reveal the presence of HIV+ human mononuclear phagocytes and multinucleated giant cells, and an increase in mouse mononuclear phagocytes and astrogliosis within the CNS (Figure 2) (Tyor et al., 1993; Persidsky et al., 1996). Additionally, human monocytes become activated in the mouse CNS and express TNF-α and IFN-α. Greater numbers of multinucleated giant cells are seen in SCID/HIVE mice compared to control mice injected with uninfected human monocytes. HIV-infected mice have significantly greater astrogliosis than uninfected mice; microgliosis is also greater in HIVE mice, but is confined to the area around HIV-infected cells. Therefore, the SCID mouse model of HIVE shares many of the pathological features seen in the human condition.

In order to model what happens in humans more completely, and to clarify the features of HIVE that lead to HAD, it was important to demonstrate cognitive deficits in this model. The Morris water maze tests learning and memory by forcing the animal to use visual cues in order to locate a submerged platform.
Uninfected controls were compared to infected mice in terms of their ability to learn the location of the platform, and, after a one week hiatus, remember the location of the platform. These studies demonstrated that the uninfected mice were able to learn the location of the platform while the infected mice were not, indicating cognitive dysfunction (Figure 3) (Avgeropoulos et al., 1998; Griffin et al., 2004). Therefore, similar to the human disease, SCID/HIVE mice develop behavioral abnormalities.

As previously mentioned, there has been some indication that viral strain plays a role in the development of cognitive deficits. We used this animal model to compare the cognitive effects of HIVada to a more neurovirulent strain, HIV-SF162. HIV-SF162 was isolated from a patient with severe HIVE and has been shown to kill neurons in vitro more efficiently than other strains (Power, 2004). SCID/HIVE mice infected with HIV-SF162 appeared to have more severe cognitive deficits than those infected with HIVada (preliminary observations).

## ANTIRETROVIRAL AGENTS

HAART is typically composed of at least three antiretroviral agents and has been shown to delay the onset of HAD and improve cognitive function in those with HAD. There are currently three classes of antiretroviral agents available and they are categorized based on their mechanism of action. Nucleoside Reverse Transcriptase Inhibitors (NRTIs) inhibit viral replication by being incorporated into the elongating strand of viral DNA, causing chain termination. Protease inhibitors prevent viral maturation. The third class of antiretroviral agents, termed nonnucleoside reverse transcriptase inhibitors (NNRTIs), bind noncompetitively to HIV reverse transcriptase to inhibit viral replication (Table 1) (Clifford, 1998). There are several other classes under investigation, including those that prevent the virus from fusing to the cell membrane and those that prevent the integration of viral DNA into the host genome (Portegies, 2002).

Recent studies have used HAART, composed of AZT (NRTI), lamivudine (NRTI), and indinavir (PI) in the SCID mouse model, to better understand whether these agents cross the BBB sufficiently to suppress HIV. In addition, suppression of CNS virus should allow better determination of the significance of viral load in the pathogenesis of this disease (Cook et al., 2005). HAART is known to decrease viral load systemically, but its effects on brain parenchymal viral load are unknown.

Some antiretrovirals are thought to have poor penetration into the CNS. Therefore, these studies began by measuring HAART levels in the brain tissue of these mice. SCID mice were infected with HIV-infected or uninfected human monocytes and were administered HAART or saline (vehicle) three times daily for one or two weeks (Cook et al., 2005). It was demonstrated that AZT, lamivudine, and indinavir are detectable in the brain, in the cases of AZT and indinavir, at therapeutic levels. These findings are somewhat surprising as protease inhibitors are thought to penetrate the BBB poorly.

To determine the effects of HAART on viral load, the percentages of HIV-infected cells (p24-positive) in the brains of SCID/HIVE mice with and without treatment were calculated. Two weeks after infection there is a significant decrease in the percentage of p24-positive cells in animals treated with HAART compared to those that were untreated. Real time PCR for viral load supports these findings. Again, two weeks of treatment resulted in a statistically significant decrease in virus, but, importantly, not complete eradication. The dosing was comparable to what is given to humans. Higher doses were also tested, but were not tolerated by the mice due to the toxicity associated with these agents. These studies indicate that HAART penetrates the brain parenchyma sufficiently to reduce viral load; however, virus is not eradicated. This may have important implications for the development of HAD in an aging population of HAART-treated individuals. Since HIV continues to reside in the brain of HAART patients, it may be able to mutate there and/or reseed the periphery.

Uninfected mice, with or without HAART, exhibited no difference in astrogliosis, indicating that HAART itself is not affecting the astrocyte population. Two weeks of treatment reduced astrogliosis in infected mice to a level that was comparable to what was seen in uninfected mice. This reduction was not observed in

### TABLE 1: ANTIRETROVIRAL AGENTS APPROVED FOR USE IN HUMANS

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<tr>
<td>Abacavir</td>
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<td>Didanosine</td>
<td>NRTI</td>
<td>TMC125, 120, and 114</td>
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<td>Lamivudine</td>
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<td>Zidovudine</td>
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<td>Nelfinavir</td>
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<td>Delavirdine</td>
<td>NNRTI</td>
<td>Lopinavir/ritonavir</td>
<td>PI</td>
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<td>Nevirapine</td>
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<td>Tipranavir</td>
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<td>Atazanavir</td>
<td>PI</td>
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<td>Emivirine</td>
<td>NNRTI</td>
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infected untreated mice, indicating that HAART does reduce some pathological features in SCID/HIVE mice. In addition, it appears that astrogliosis may be an important marker and contributor to the pathogenesis of HIVE.

The studies described, which examine HAART in SCID/HIVE mice have contributed to our understanding of HAART penetration into brain, its effects on viral load, and resultant pathology. Ongoing studies are examining whether HAART attenuates the behavioral abnormalities seen in SCID mice with HIVE.

CONCLUSION

Despite significant advances in HIV research and treatment, our understanding of HIV infection of the brain is still incomplete. Clinical information, including neuropsychological testing and MRI data, as well as pathological studies, suggest that the frontal cortex, basal ganglia, and hippocampus are important neuroanatomical areas involved in HAD. Recent studies utilizing a SCID mouse model of HIVE indicate that CNS viral load determines the severity of astrogliosis and these are likely important features in the pathogenesis of HAD. While clinico-pathological human studies suggest viral strain is important in the pathogenesis of HAD, SCID mouse HIVE studies have led to mixed conclusions. Since HAART does not eradicate virus in the brain, the CNS is a reservoir of HIV. Therefore, determining the importance of strain and viral mutations in the pathogenesis of HAD should steer future research efforts.

ACKNOWLEDGEMENTS

The research was supported by a grant from the National Institutes of Health. (R01 MH62697-05 and R01 DA11870-01). The authors would like to thank Chris Power for supplying HIV-SF162.

REFERENCES


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