Perspective

Neurologic Complications of HIV Infection in the Era of Antiretroviral Therapy

Neurologic complications in persons with HIV infection are less severe in the era of potent antiretroviral therapy but remain highly prevalent. Prior to the use of antiretroviral therapy, opportunistic infections of the central nervous system (CNS) and CNS malignancy were common. Progressive multifocal leukoencephalopathy (PML), however, remains a diagnostic challenge in HIV-infected individuals, and no effective antiviral treatment for PML is currently available. Primary neurologic complications of acute HIV infection include aseptic meningitis and acute inflammatory demyelinating polyneuropathy. Among the neurologic complications of chronic HIV infection, HIV-associated neurocognitive disorders (HAND) remain most prevalent. The use of antiretroviral therapy has greatly reduced the severity of HAND, under which progressive HIV-associated dementia once predominated, to a milder chronic form of potentially disabling neurocognitive impairment. The persistence of HAND in individuals with virologic suppression suggests a need for adjunctive therapies for limiting its morbidity. This article summarizes a presentation by Dennis Kolson, MD, PhD, at the IAS–USA continuing education program, Improving the Management of HIV Disease, *held in Chicago, Illinois, in May 2017.*

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In the era of potent antiretroviral therapy, neurologic complications of HIV infection are less severe but are still surprisingly common. Before the availability of antiretroviral therapy, approximately 20% of HIV-infected persons died with HIV-associated dementia (HAD), the most severe form of HIV-associated neurocognitive disorder (or disorders; HAND),[1] and most individuals who died with HAD and underwent autopsy were found to have HIV encephalitis.[2] HAD is now observed in a much smaller proportion of persons (1%-4%), and HIV encephalitis is, essentially, never seen at autopsy.

Before the availability of antiretroviral therapy, HIV-infected persons were also at increased risk for severe complications of opportunistic infections (OIs) such as cytomegalovirus infection, toxoplasmosis, and progressive multifocal leukoencephalopathy (PML). Nonetheless, in the era of suppressive antiretroviral therapy, there remains a high prevalence of primary manifestations (those not due to OIs) of HIV infection, including persistent HAND and peripheral neuropathy. Although severe HAND, in the form of HAD, is much less common, a less severe but potentially disabling form termed mild neurocognitive disorder (MND) is seen in approximately 15% of individuals with virologic suppression.[1] The prevalence of peripheral neuropathy (approximately 30%-40% with the earliest antiretroviral regimens), particularly the classic distal symmetric polyneuropathy (DSP), has been reduced with the use of less toxic antiretroviral regimens.

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Dynamics of HIV Infection in the Central Nervous System

HIV enters the central nervous system (CNS) early in the course of infection, within days to 1 or 2 weeks of systemic inoculation. A major entry mechanism is likely transendothelial migration of infected CD4+ T lymphocytes, and another potential entry mechanism is migration of infected monocytes.[3,4] Within approximately the first 4 months of systemic infection, HIV-infected T cells may establish a compartmentalized reservoir in which the virus can evolve independently from virus in plasma, and there is evidence of the emergence of macrophage-tropic virus within the first 2 years of HIV infection. Compartmentalization of virus within T cells in the CNS is estimated to occur in 20% to 30% of HIV-infected persons during this time.[4] Monocyte-derived macrophages (MDMs), which are found primarily in perivascular areas, can also harbor virus that is readily detectable in autopsied brains of individuals who died with HIV/AIDS.[5] HIV replication in MDMs is well documented.[6] Whether this potential CNS compartmentalized HIV reservoir (perivascular macrophages) is established through transendothelial migration of infected blood monocytes, infection through entry of free virions, or cell-mediated virus transfer is controversial.[6,7] Evidence suggests that MDMs can phagocytose HIV-infected T cells, which has been suggested to lead to a nonproductive "infection" without the release of infectious virions.[8,9]

Viral replication within the CNS is associated with production of proinflammatory cytokines and neurotoxins, including glutamate and reactive oxygen species, which indicates a state of oxidative stress that likely drives HAND. Uncontrolled HIV replication is associated with more severe HAND, and well-controlled HIV replication (suppression) is associated with less severe HAND. In the pre–antiretroviral therapy era, uncontrolled CNS HIV replication was associated with profound neuronal apoptosis and dropout in association with HIV encephalitis. In the era of suppressive antiretroviral therapy, these characteristic pathologic findings in the CNS are no longer observed, suggesting that microscopic structural alterations or functional physiologic alterations in neuronal populations might contribute substantively to the clinical symptomatology of HAND.[2] As with systemic HIV infection in the context of suppressive antiretroviral therapy, there is evidence for immune activation, inflammation, and oxidative

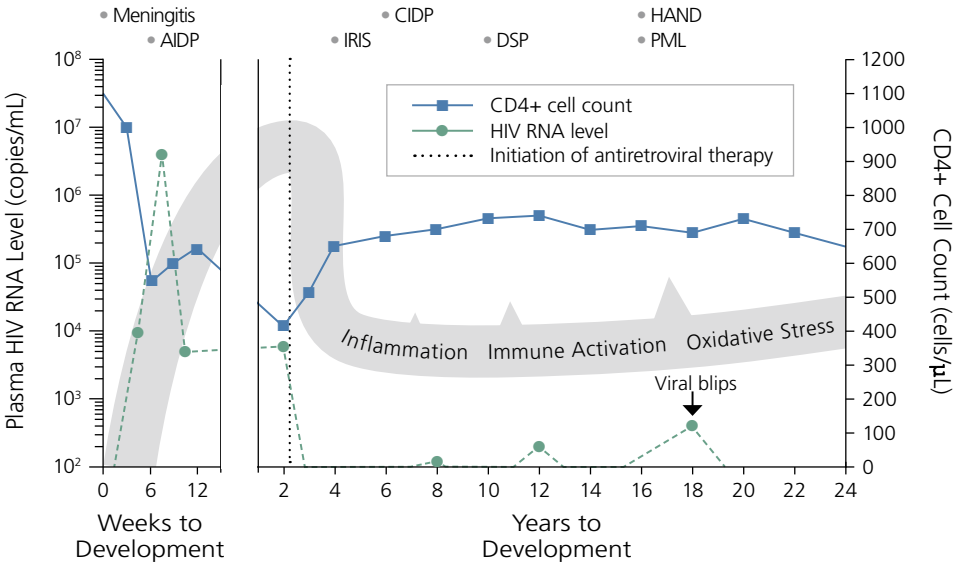

Figure. The primary neurologic complication of acute HIV infection prior to seroconversion is meningitis. Acute inflammatory polyneuropathy (AIDP) occurs around the time of seroconversion. Later neurologic complications include immune reconstitution inflammatory syndrome (IRIS), which is initiated by introduction of antiretroviral therapy, chronic inflammatory polyneuropathy (CIDP), distal symmetric polyneuropathy (DSP), HIV-associated neurocognitive disorders (HAND), and progressive multifocal leukoencephalopathy (PML). The grey ribbon depicts the detection of biomarkers of inflammation, immune activation, and oxidative stress in the cerebrospinal fluid during the course of infection. The relative time course for the development of these disorders is shown on the x-axis. The grey ribbon depicts the detection of biomarkers of inflammation, immune activation, and oxidative stress in the cerebrospinal fluid during the course of infection The relationship to plasma HIV RNA level and CD4+ cell count are shown in the left and right y-axes, respectively.

stress in the CNS of individuals with virologic suppression. "Blips" of viral replication within the CNS compartment (cerebrospinal fluid) are detected in approximately 15% of individuals on suppressive antiretroviral therapy, as they are during systemic infection, and such blips are associated with biomarkers of monocyte-macrophage activation.[10] The possible role of blips in the pathogenesis of HAND remains unclear.

Early Neurologic Manifestations of Acute HIV Infection

Acute CNS HIV infection can be associated with aseptic meningitis and the rarer acute inflammatory demyelinating polyneuropathy (AIDP) syndrome (Figure). Aseptic meningitis typically occurs within the first 10 to 20 days after systemic HIV infection in up to 25% of individuals.[11] Classic symptoms of aseptic meningitis are headache, fever, and stiff neck, which are self-limited over a 2- to 4-week period. Individuals are generally HIV antibody negative during this time,[12] and the diagnosis of HIV infection is often missed in those presenting with such symptoms.

Acute Inflammatory Demyelinating Polyneuropathy

AIDP, also called Guillain-Barré syndrome, occurs in less than 1% of HIV-infected individuals and is likely to go undiagnosed in the primary care setting. Onset of AIDP is most often observed during HIV seroconversion 3 to 4 weeks after initial infection, and following the symptoms of aseptic meningitis (Figure).[13,14] Typically, AIDP progresses rapidly as a uniphasic illness over a period of days to fewer than 4 weeks. AIDP is characterized by a white blood cell count in the cerebrospinal fluid of 50/μL or lower and an elevated protein level. It presents as ascending symmetric motor weakness of the distal extremities, with potentially life-threatening respiratory and autonomic dysfunction occurring in up to one-third of individuals.

Treatment of AIDP in HIV-infected individuals includes plasmapheresis and the administration of intravenous γ-globulin. Emerging evidence suggests that short-term treatment with corticosteroids may be effective when AIDP occurs in the setting of immune reconstitution inflammatory syndrome (IRIS) after initiation of antiretroviral therapy.[15,16]

Chronic Neurologic Manifestations of HIV Infection

Chronic neurologic complications of HIV infection include chronic inflammatory demyelinating neuropathy (CIDP), DSP, IRIS, PML, and HAND (Figure). Each of these complications is discussed below.

Chronic Inflammatory Demyelinating Neuropathy

CIDP is typically observed after 1 or more years of HIV infection (Figure).[14] The condition is marked by motor paralysis that may progress slowly over 8 or more weeks or express a relapsing or remitting course of exacerbations and remissions. CIDP is a demyelinating-remyelinating disease that, in biopsy of peripheral nerves, shows evidence of myelin loss followed by partial remyelination in what is described pathologically as "onion bulb formation," reflecting new layers of myelin at the nerve terminal.

Treatment of CIDP includes plasmapheresis and administration of intravenous γ-globulin or corticosteroids, and responses to these treatments among HIV-infected individuals are generally similar to those among uninfected individuals.[14] However, data from a recent study suggest that corticosteroids might be somewhat more effective among HIV-infected individuals than among uninfected individuals.[17]

Distal Symmetric Polyneuropathy

The most common neuropathic problem in people with HIV infection, whether or not they are taking antiretroviral

therapy, is classically recognizable DSP.[18,19] DSP is thought to have at least 2 etiologies: 1) peripheral nerve injury associated with replication of virus in macrophages within the dorsal root ganglia or within macrophages in the peripheral nerves[20]; and 2) neurotoxic effects of antiretroviral drugs. A primary culprit in the latter regard was the nucleoside analogue reverse transcriptase inhibitor stavudine, although other nucleoside reverse transcriptase inhibitors (didanosine and zalcitabine) and, occasionally, protease inhibitors (indinavir, saquinavir, and ritonavir) are also associated with DSP.[21] Although the prevalence of DSP resulting from the toxic effects of antiretroviral therapy has decreased with the use of newer treatments, DSP persists in some individuals, perhaps because of damage resulting from residual effects of HIV replication or past use of neurotoxic antiretroviral therapy.[14,21]

In contrast to demyelinating polyneuropathies, this axonal neuropathy is characterized by burning pain in the distal extremities following a stocking-glove distribution and is often without motor manifestations. DSP is easily distinguished from demyelinating neuropathies in nerve conduction studies. However, DSP is often mistaken for diabetic neuropathy in people with type 2 diabetes.

DSP is not readily treatable. Antiepileptic drugs (eg, gabapentin, lamotrigine, and pregabalin) have been used to treat DSP, but evidence of the benefits of such treatments is weak. However, single-dose applications of high-dose, topical capsaicin to the soles and sides of affected feet reportedly provided relief in up to 30% to 40% of individuals over a 12-week period.[22] Thus, several annual treatments of high-dose, topical capsaicin may be appropriate for some people.

Immune Reconstitution Inflammatory Syndrome

IRIS in the CNS is most common approximately 1 to 6 months after the initiation of suppressive antiretroviral therapy (Figure), particularly in individuals who begin therapy with a lower CD4+ cell count and higher viral load.[23] Findings can be vague and symptoms may range from mild (eg, headaches and some dizziness) to very severe (eg, encephalopathy, disorientation, delirium, coma, and stupor). CNS IRIS results from heightened immunologic and inflammatory responses, generally in the setting of a history of infection with opportunistic pathogens. However, IRIS can also occur in HIV-infected individuals with exposed CNS antigens from other causes, as in the case of multiple sclerosis[24] or stroke.[25] Thus, the diagnosis of CNS IRIS may be missed in individuals with no history of OIs. The prevalence of CNS IRIS is approximately 1% among all HIV-infected individuals initiating antiretroviral therapy, but up to 30% or higher in those initiating therapy with a history of concurrent or antecedent cryptococcal meningitis, tuberculosis, or PML.[23,26]

CNS IRIS is diagnosed using magnetic resonance imaging (MRI) of the brain, with administration of intravenous gadolinium to detect regional defects in the blood-brain barrier consistent with inflammation. Treatment for IRIS-related complications includes supportive care, treatment of an underlying OI if one is present, and abscess drainage in cases of cryptococcal meningitis with increased intracranial pressure. Treatment with steroids has reportedly been helpful, and available evidence suggests that intravenous methylprednisolone for several days up to a week followed by oral prednisone tapered over the course of 2 to 3 weeks may be beneficial.[23] Results from the COAT (Cryptococcal Optimal ART Timing) trial demonstrated that delaying antiretroviral therapy after the initial diagnosis and treatment of cryptococcal meningitis substantially reduced mortality from all causes, including CNS IRIS.[27] Recent HIV treatment guidelines recommend delaying initiation of antiretroviral therapy at least until after completion of antifungal induction therapy (2 weeks)[28] and even through completion of consolidation therapy (10 weeks) for individuals with increased intracranial pressure or low white blood cell counts in cerebrospinal fluid.[29]

Progressive Multifocal Leukoencephalopathy

Asymptomatic infection with JC virus, which causes PML, is widespread in the general population (70%-80%), and among HIV-infected populations not receiving antiretroviral therapy, the prevalence of PML is approximately 4%. With suppressive antiretroviral therapy, the incidence of PML has decreased from approximately 10 cases per 1000 person-years to 1 case per 1000 person-years,[30] with a 1-year fatality rate of approximately 30% in antiretroviral therapy–experienced individuals.

The diagnosis of PML requires a high level of clinical suspicion, as its clinical symptoms and radiographic features are sometimes mistaken for an acute stroke. PML is characterized by changes in white matter that can often be observed early in the occipital areas of the brain, although other regions are also affected. PML lesions tend to be large and expand over time, unlike those observed with stroke. PML is sometimes confused with stroke because of the slow evolution of hemiparesis in association with memory loss, slurred speech, and dysarthria, which mimic a slowly evolving stroke. However, in clinical presentation, PML is accompanied by seizures in 15% to 30% of cases, in comparison with classic cortical stroke, in which seizure frequency is estimated at approximately 3% to 6%.[31] Further, PML is often accompanied by visual symptoms including blind spots in visual fields, reflecting occipital predominance.

There are no known effective direct antiviral treatments for PML; studies of treatment with intrathecal cytosine arabinoside and cidofovir have failed to show benefit. However, reconstitution of immune function with suppressive antiretroviral therapy is associated with increased long-term survival.[30]

HIV-Associated Neurocognitive Disorders

HAND and DSP remain the most common HIV-associated neurologic complications in the era of suppressive antiretroviral therapy. HAND is believed to largely reflect the persistence of immune activation, inflammation, and oxidative stress

in the CNS despite viral suppression. The risk of developing HAND might increase with age in the HIV-infected population.[1] Studies of cerebrospinal fluid and plasma in individuals with HAND have shown elevated low-molecular-weight neurofilament in the CNS, indicating neuronal damage, and elevated soluble CD163 and neopterin (markers of monocyte-macrophage activation) in plasma and the CNS. Historically, the best plasma biomarker for risk of HAND has been nadir CD4+ cell count, but soluble CD163 may take its place.

Diagnosis of HAND is based on formal neuropsychologic testing using the Frascati criteria[32] and assessment of activities of daily living. HAND often goes undiagnosed in individuals who present without overt symptoms of dementia. Although the prevalence of HIV-associated dementia has declined in the era of suppressive antiretroviral therapy, MND (the less severe form of HAND) still functionally impairs approximately 20% of individuals with virologic suppression.[1] Individuals with MND, by definition, suffer cognitive dysfunction and functional impairment in certain activities of daily living. There are no typical MRI findings for HAND, although approximately one-third of individuals exhibit abnormalities in white matter, distinct from those seen in PML, with or without brain atrophy.

There are conflicting reports on the effectiveness of using antiretroviral regimens with increased CNS antiviral efficacy to treat or prevent HAND, using a scaling system that estimated antiviral activity of antiretroviral drugs within the CNS compartment (CNS penetration effectiveness [CPE]).[33] There are currently no clear recommendations for altering antiretroviral regimens based on CPE.[34] That antiretroviral drugs may directly induce oxidative stress and neuronal damage in the CNS, as they have been shown to do in studies in vitro, remains a concern.

Intensification of antiretroviral therapy may currently be the best hope for managing and perhaps decreasing the prevalence of HAND. Intensification of antiretroviral therapy with maraviroc led to improvements in neurocognitive dysfunction over a 12-month period.[35] The large AIDS Clinical Trials Group 5324 study, which is currently enrolling participants, will examine the effects of intensification of antiretroviral therapy with dolutegravir and maraviroc on neurocognitive performance in individuals with HAND.

Adjunctive Neuroprotective Strategies

The future of treatment for HAND is likely to involve adjunctive therapies to control neuroinflammation and oxidative stress, in addition to antiretroviral therapy. Studies of the brains of individuals who have died with HIV infection have identified what might be a unique brain "signature" in those with HAND: a deficiency of the cytoprotective enzyme heme oxygenase-1.[36] Heme oxygenase-1 is a rapidly inducible endogenous cytoprotective enzyme that serves to reduce cytotoxic injury in cells undergoing oxidative stress from a variety of insults. Therapeutic strategies for increasing heme oxygenase-1 expression in several inflammatory diseases are being pursued in preclinical and in vitro studies. Other adjunctive neuroprotective strategies for HAND that target pathways of inflammation and immune activation have been suggested.[1]

Summary

The acute neurologic complications of HIV infection (eg, meningitis and AIDP) have not changed since the availability of suppressive antiretroviral therapy, although several of the chronic neurologic complications have changed. Opportunistic CNS infections, including PML, are now rare, although PML risk might increase with advancing age. DSP from the toxic effects of antiretroviral drugs has decreased, but DSP attributed to the damaging effects of HIV replication (pre– or post–antiretroviral therapy) in the dorsal root ganglia or peripheral nerves might represent a separate and persistent contributor to this condition. HAND is less severe with suppressive antiretroviral therapy but is still common enough to represent a significant morbidity among HIV-infected individuals, and its prevalence might increase with the advancing age of this population.

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