Human Immunodeficiency Virus–Associated Peripheral Neuropathies

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Peripheral neuropathy has emerged as the most common neurologic complication of human immunodeficiency virus (HIV) infection. It will continue to play an important role in HIV infection given the fact that HIV-infected individuals are living longer, are at risk of long-term metabolic complications, and face an increasing exposure to potentially neurotoxic antiretroviral drugs. We review the various types of peripheral neuropathy that have been associated with HIV infection, including distal symmetrical polyneuropathy, toxic neuropathy from antiretroviral drugs, diffuse infiltrative lymphocytosis syndrome, inflammatory demyelinating polyneuropathies, multifocal mononeuropathies, and progressive polyradiculopathy.

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AIDS = acquired immunodeficiency syndrome; CMV = cytomegalovirus; DILS = diffuse infiltrative lymphocytosis syndrome; DSP = distal symmetrical polyneuropathy; IDP = inflammatory demyelinating polyneuropathy; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; NRTI = nucleoside reverse transcription inhibitors; PN = peripheral neuropathy

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The availability of potent antiretroviral drugs and their use in 3 or more combination regimens, highly active antiretroviral therapy (HAART), have led to a substantial decline in the morbidity and mortality associated with human immunodeficiency virus (HIV) infection.[1] Although a similar overall decline has occurred in the incidence and prevalence of central nervous system complications,[2,3] peripheral neuropathy (PN) continues to be a common neurologic complication at every stage of HIV infection. The spectrum of peripheral involvement in HIV infection includes distal symmetrical polyneuropathy (DSP), toxic neuropathy from antiretroviral drugs, diffuse infiltrative lymphocytosis syndrome (DILS), inflammatory demyelinating polyneuropathies (IDPs), multifocal mononeuropathies, and progressive polyradiculopathy. Diagnosis and treatment of PN in the HAART era represent a challenge even for expert neurologists and consultants in infectious diseases because of the overlap of clinical symptoms, complexity of treatment choices, and a possible abnormal presentation of symptoms of PN during immune reconstitution, when the CD4 T-lymphocyte count is rising.[3]

In this review, we discuss the various types of PNs associated with HIV infection, including their clinical presentation, pathogenesis, and treatment. Data for this review were identified by searches of the MEDLINE database for articles published in the English-language literature since 1966 using *HIV, peripheral neuropathy, polyneuropathy, distal symmetrical polyneuropathy, inflammatory demyelinating polyneuropathy, mononeuropathy,* and *polyradiculopathy* as keywords or text words. When applicable, we reviewed references cited in relevant reports and studies. We also included relevant microscopy and electron microscopy images from our own files.

DISTAL SYMMETRICAL POLYNEUROPATHY

Distal symmetrical polyneuropathy is the most frequent form of neuropathy in HIV-1 infection. It is detected by clinical examination in 30% of infected patients[4] and in almost 100% of cases at autopsy examination of individuals with acquired immunodeficiency syndrome (AIDS).[5] In one study, DSP showed a significant decline in prevalence from 42.5% in 1995-1996 to 34.4% in 1997-1998.[6] In contrast, the prevalence of suspected drug-induced polyneuropathy increased to 31% compared with 20% in 1995-1996. Moreover, after the introduction of HAART, DSP was not associated with increased HIV-1 load or decreased CD4 T-cell count.[7] In a recent HIV-1 outpatient cohort study, 13.1% of 2515 patients received a clinical diagnosis of DSP,[8] with a decreasing incidence after the introduction of HAART. The risk of developing DSP increased during the initial period of drug therapy, especially when therapy was started in patients with low CD4 lymphocyte counts (50-90 cells/μL) and higher HIV-1 load (>10,000 copies/mL). The authors suggested that disease progression and host factors have a strong independent association with an increased risk of the development of DSP but also may predispose individuals to the neurotoxic effects of antiretroviral medications. HAART lessens disease progression, improves immunity, and widens the ratio of therapeutic to toxic effects of individual antiretroviral drugs, resulting in a significantly lower risk of developing DSP.

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The clinical presentation of DSP is painful feet, with most patients complaining of hyperpathia localized in the feet. Muscle weakness is usually mild or absent. Neurologic examination reveals depressed or absent ankle tendon reflexes in 96% to 100% of cases.[4,9] Sensations of pain and temperature are impaired in the distal portion of the legs in 85% of patients.[9] The electrophysiologic findings show small or absent sural sensory nerve activation potentials. Reduction in the size of intrinsic foot compound muscle action potentials is less sensitive than sensory nerve activation potentials. Nerve conduction studies usually confirm a length-dependent axonal polyneuropathy, distinguishing between DSP and inflammatory demyelinating neuropathy. Needle electromyography shows acute or chronic partial denervation of distal lower limb muscles.[9]

The neuropathologic features of sensory nerves are loss of myelinated and unmyelinated fibers with axonal degeneration and macrophage activation. Secondary aspects of demyelination and epineurial vascular infiltration are rarely reported.[10] In autopsy series, fiber loss and wallerian degeneration are more evident in distal than in proximal regions of peripheral nerves.[11] The dorsal root ganglia frequently contain small numbers of degenerating neurons with macrophage and lymphocyte activation. Direct HIV-1 infection of nerve fascicles or dorsal root ganglia neurons has been shown in a small number of cases.[12,13]

The pathogenesis of DSP, although not well known, is thought to be multifactorial. A significant role may be due to exposure to neurotoxic antiretroviral nucleoside reverse transcription inhibitors (NRTIs) or to other classes of drugs less commonly used during HIV-1 infection, such as vincristine, isoniazid, ethambutol, and dapsone.[14] In patients receiving NRTIs, therapy interferes with DNA synthesis and causes mitochondrial abnormalities.[15] Pathogenetic mechanisms remain uncertain for individuals without toxic exposure. Although HIV-1 may play a direct role in the PN, evidence of the presence of the virus in peripheral nerves or in dorsal root ganglia is limited to a few occasional case reports.[12,13] Rarely, vitamin B_{12} deficiency or DILS has been implicated.[16]

Current therapies for DSP are limited to symptomatic treatment of foot pain. The pharmacological approach to symptomatic treatment of pain in DSP includes the use of different classes of drugs in successive steps: nonsteroidal anti-inflammatory drugs, topical analgesics (lidocaine and capsaicin), tricyclic antidepressants (amitriptyline and desipramine), antiepileptic agents (gabapentin and lamotrigine), and narcotic analgesics (oxycodone, morphine, and fentanyl patches). In clinical practice, a combination of several drugs with different mechanisms of action is frequently needed to alleviate pain and functional disability.[17] However, data from controlled studies showing the efficacy of many of these drugs are lacking. Recent placebo-controlled trials confirm the effectiveness of both gabapentin and lamotrigine in reducing pain in patients with HIV-1–associated DSP.[18,19] In another randomized controlled trial, 5% lidocaine gel failed to alleviate DSP pain.[20] Studies of nerve growth factor–treated patients[21] and preliminary data with prosaptide, a polypeptide analgesic with neuroregenerative properties, suggest some benefit in reducing neuropathic pain.[17] In another randomized, placebo-controlled study, neither acupuncture nor amitriptyline was more effective than placebo in relieving pain caused by HIV-related PN.[22]

TOXIC NEUROPATHY FROM ANTIRETROVIRAL DRUGS

A clinical picture resembling DSP is frequently noted during antiretroviral therapy. With the advent of HAART, the incidence of DSP has increased largely from the use of the NRTIs didanosine, zalcitabine, and stavudine. The toxic effect of NRTIs is dose dependent and is estimated to occur in 15% to 30% of patients receiving each of these drugs.[14,23,24] Recent preliminary data, reported at the 56th Annual Meeting of the American Academy of Neurology, show an increased risk of DSP in patients treated with 3 protease inhibitors: indinavir, saquinavir, and ritonavir.[25] These drug-induced neuropathies may be due to toxicity that results from inhibition of mitochondrial DNA polymerase.[15] No differences in the severity of the clinical, electrophysiologic, or morphologic features have been noted between NRTI-treated or untreated patients. Management of antiretroviral-induced neuropathy begins with excluding other potential causes, such as chronic alcoholism, uremia, vitamin B_{12} deficiency, and diabetes mellitus. Further management options include removal of the putative causative drug and/or prescribing symptomatic treatment similar to that described for DSP.

A syndrome characterized by hyperlactatemia, nausea, vomiting, hepatomegaly, and progressive muscle weakness was recently described in association with NRTI treatment.[26] In this disorder, named *HIV-associated neuromuscular weakness syndrome*, motor weakness develops rapidly in days or weeks and evolves in some cases into respiratory failure and death, mimicking Guillain-Barré syndrome. Simpson et al,[27] in a series of 69 patients affected by this disorder, found a variable range of neuromuscular involvement, from progressive sensorimotor polyneuropathy with electrophysiologic and pathologic predominant axonal damage to myopathy with muscular inflammatory infiltration. The mortality rate was 13%. The pathophysiologic mechanism of HIV-associated neuromuscular weakness syndrome is thought to be related to the mitochondrial toxicity of prolonged NRTI (particularly

stavudine) therapy, although immune-mediated mechanisms may also be involved.

DIFFUSE INFILTRATIVE LYMPHOCYTOSIS SYNDROME

Persistent CD8 lymphocytosis, named *diffuse infiltrative lymphocytosis syndrome* is characterized by a persistent peripheral blood polyclonal CD8 lymphocytosis and by visceral CD8 T-cell infiltration, including salivary glands, lungs, kidneys, gastrointestinal tract, and peripheral nerves.[16,28,29] Infiltration of the salivary glands produces a Sjögren-like disorder. Patients with DILS tend to have higher CD4 cell counts, fewer opportunistic infections, and longer survival times than typical HIV-infected patients. Clinically, DILS presents as acute or subacute painful multifocal, most often symmetrical, neuropathy. Electrophysiologic studies show axonal neuropathy. Nerve biopsy specimens are characterized by marked angiocentric CD8 infiltrates and abundant expression of HIV p24 protein without vessel wall necrosis. The treatment of DILS consists primarily of standard antiretroviral therapy and/or corticosteroids.

INFLAMMATORY DEMYELINATING POLYNEUROPATHIES

Inflammatory demyelinating polyneuropathies are disorders with acute or chronic evolving weakness in arms and legs and minor sensory symptoms. Although data from large series or controlled trials are lacking, the clinical features and the disease course of patients with acute or chronic IDP appear to be similar in HIV-1–positive and HIV-1–negative patients. Although acute and chronic IDPs occur with increasing frequency in HIV-1–infected patients, they remain rare complications of HIV-1 infection. In acute IDP, the nadir of neurologic signs is reached within 4 weeks after onset, whereas in chronic IDP the evolution of neurologic deficit lasts more than 8 weeks and may be progressive or relapsing and remitting. The first case of acute IDP associated with AIDS was described in 1985.[30] Three patients with acute IDP preceding the diagnosis of AIDS were described by Cornblath et al.[31] Other successive studies confirmed the observation that acute IDP occurs early in HIV-1 infection before severe immunosuppression.[32,33] In a large series of 32 patients with acute IDP in Zimbabwe, all 16 HIV-1–positive patients developed acute IDP before the diagnosis of AIDS.[34] In the study by Brannagan and Zhou,[35] of 10 patients with acute IDP with HIV-1 infection, 40% developed acute IDP after onset of AIDS (CD4 T-cell count <200/μL). This study also showed that cerebrospinal fluid pleocytosis was not always present in HIV-1–associated acute IDP. Recurrence of acute IDP and evolution to chronic IDP were observed in 3 of these 10 patients. Neurophysiologic examination shows slow conduction, increase in distal motor latencies, increase of F-wave latency, and partial conduction blocks outside entrapment sites, suggesting demyelinating neuropathy. High protein content and, at variance with non–HIV-1–associated IDPs (in which the lymphocyte count is always <10 cells/μL), mild lymphocytic pleocytosis are present in the spinal fluid.[31] Pathologic examination of peripheral nerves in chronic IDP shows segmental demyelination with onion bulb formations, macrophage activation and infiltration by mononuclear cells of nerve fascicles, and endoneurial edema. Treatment options for HIV-associated acute and chronic IDPs are similar to those used in HIV-negative persons. The treatment response also appears to be similar, although data from large series and controlled trials are lacking. Treatment of acute IDP includes high-dose intravenous immunoglobulins or plasmapheresis. The course of chronic IDP generally improves with oral prednisone; high-dose immunoglobulins or plasmapheresis is used for recurrences.[36,37]

MONONEURITIS MULTIPLEX

Mononeuritis multiplex is a rare complication that occurs in either early or late stages of HIV-1 infection.[38] When mononeuritis multiplex occurs early in HIV-1 infection, it is often the result of a self-limited dysimmune neuropathy or vasculitis. In patients with long-standing HIV-1 infection and CD4 cell counts less than 50/μL, an association with cytomegalovirus (CMV) infection has frequently been noted. Mononeuritis multiplex has also been associated with varicella zoster[39] and hepatitis C infections.[40] The clinical setting of mononeuritis multiplex is characterized by symptoms and signs of sensory involvement, with numbness and tingling in distribution of one peripheral nerve trunk. Sequential sensory and motor involvement of other noncontiguous nerves evolves over days and weeks. The initial multifocal and random neurologic features may progress to symmetrical neuropathy. Some patients with vasculitis present at onset with distal symmetrical neuropathy. The diagnosis of mononeuritis multiplex is supported by electrophysiologic examination that reveals a multifocal pattern of reduction in evoked sensory and motor compound muscle action potential amplitudes.

Vasculitis

Virtually every pattern of vasculitis of small, medium, and large vessels has been encountered in HIV-1 infection.[41] Vasculitis of the peripheral nerve can occur either as an isolated process or, more commonly, as a manifestation of a systemic disease. Vasculitis of the peripheral nerve is a
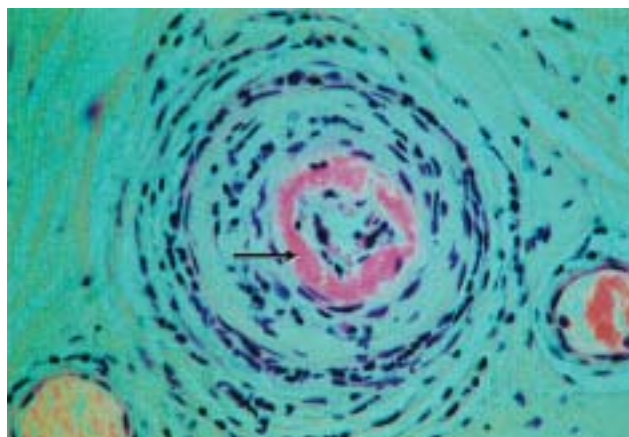
FIGURE 1. Necrotizing vasculitis with infiltrate of inflammatory cell and fibrinoid necrosis (arrow) of epineurial arteriolar wall (paraffin section, hematoxylin-eosin, original magnification ×310).
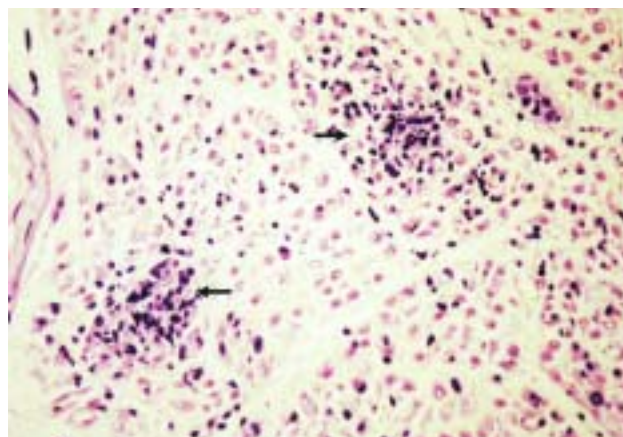

FIGURE 2. Infiltrates of mononuclear and polymorphonuclear cells (arrows) in cytomegalovirus-infected nerves (paraffin section, hematoxylin-eosin, original magnification ×185).

rare event in HIV-1–infected patients, occurring in 0.3% to 1.0% of patients with AIDS.[42] In contrast to the situation in the pre-HAART era, vasculitic damage in the peripheral nervous system may now present with clinical features of DSP.[43,44] Peripheral nerve examination shows variable loss of myelinated axons and ongoing axonal degeneration with focal distribution in different fascicles. Perivascular inflammatory cell infiltration (Figure 1) and fibrinoid necrosis of small epineural blood vessels are observed. Vasculitis is treated w ith corticosteroids or intravenous immunoglobulin.[44]

CMV INFECTION

Cytomegalovirus disease is a recognized opportunistic infection in HIV-infected patients with low CD4 cell counts

FIGURE 3. Cytomegalovirus particles (arrows) in cytoplasm of endoneurial cell (electron micrography, original magnification ×37,500).

(<50 cells/μL). The spectrum of CMV disease in HIV-infected patients includes retinitis, gastrointestinal involvement, hepatitis, pneumonia, epididymitis, cervicitis, adrenalitis, and pancreatitis. Central nervous system and peripheral nerves may also be infected with CMV; when the peripheral nerve is affected, the clinical pattern may be mononeuritis multiplex, polyradiculopathy, or a mixture of 2 patterns.[35]

Electrodiagnostic findings confirm a multifocal nerve involvement. Peripheral biopsy specimen of the affected nerve shows an infiltrate of polymorphonuclear cells harboring CMV in nerve fascicles (Figure 2) and CMV-infected endoneurial cells that contain viral inclusions (Figure 3). Treatment consists of the antiviral drugs ganciclovir, foscarnet, and cidofovir.

PROGRESSIVE POLYRADICULOPATHY

Progressive polyradiculopathy is an uncommon but well-described complication of HIV infection. No accurate estimates exist of the incidence of progressive polyradiculopathy associated with HIV infection. Fuller et al[42] identified 54 patients (approximately 4%) with peripheral nerve syndromes among a cohort of 1500 HIV-infected patients followed up for 15 months before the introduction of HAART. Only 2 patients (0.1%) had progressive polyradiculopathy. The incidence of HIV-associated progressive polyradiculopathy is thought to have declined in the era of HAART. However, no reliable and specific estimates are available. Maschke et al[6] performed a retrospective analysis of the records of HIV-positive patients under treatment since the introduction of HAART and compared the incidence and prevalence of neurologic disorders in 1995-1996 with 1997-1998. They reported that the incidence and prevalence of HIV-associated neurologic disor-
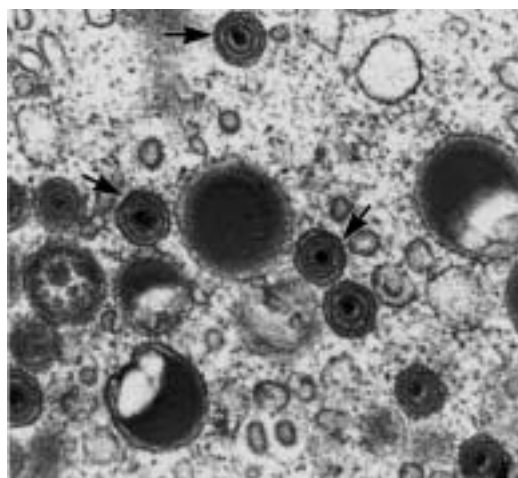
ders and opportunistic central nervous system infections decreased after introduction of HAART, but specific data on progressive polyradiculopathy were not provided. Progressive polyradiculopathy associated with HIV is usually attributed to CMV infection.[35,45-48] However, it can be caused by other conditions, including lymphoma,[49] syphilis,[50,51] mycobacterial infections,[52,53] herpes simplex virus,[54,55] and cryptococcus.[56]

Progressive polyradiculopathy usually occurs in patients with advanced HIV disease and in patients with low CD4 cell counts. The onset is subacute, and the course extends for days to weeks. The earliest symptoms are usually low back pain with radiation into one leg followed by progressive leg weakness. If not promptly identified and treated, the symptoms rapidly progress to a flaccid paraplegia with bowel and bladder incontinence. Upper extremities may be involved late in the course.[35,45-48] The cerebrospinal fluid findings in patients with CMV-related progressive polyradiculopathy are typically characterized by a polymorphonuclear pleocytosis, elevated protein level, and hypoglycorrhachia.[57,58] Although CMV is rarely recovered by conventional cell culture, polymerase chain reaction amplification of CMV DNA has proved to be a rapid and sensitive tool to detect CMV in the spinal fluid.[59] Tuberculosis usually presents with lymphocytic pleocytosis but can also present with polymorphonuclear predominance.[52,53] Lymphocytic pleocytosis was noted in a case of polyradiculopathy caused by lymphoma.[49] Syphilis presents with cerebrospinal fluid polymorphonuclear pleocytosis, but the test result for cerebrospinal fluid VDRL is positive.[50,51]

The major electrophysiologic abnormalities seen are widespread denervation in paraspinal muscles, reflecting axonal loss in lumbosacral roots with later denervation potentials in the leg muscles.[47,53] Nerve conduction study results are usually normal. Although it may show enhancement of lumbosacral meninges and nerve roots, the main utility of magnetic resonance imaging is to exclude focal mass lesions that may be compressing the cauda equina.[53,60]

Several pathologic features have consistently been reported in autopsy studies of patients with progressive polyradiculopathy.[35,45,48] These features include marked inflammation and necrosis of the dorsal and ventral nerve roots with cytomegalic inclusions detectable in endothelial cells and nerve parenchyma. In severe cases, vascular congestion, edema, and parenchymal necrosis have been noted. In progressive radiculopathy caused by lymphoma, infiltration of the anterior and posterior roots, including cauda equina, has been observed.[49]

Current choices for the treatment of CMV disease are ganciclovir, foscarnet, and cidofovir. The most experience in the treatment of CMV-related progressive polyradiculopathy is with the use of intravenous ganciclovir.[61-64] However, treatment success with foscarnet has been reported. Combination treatment with both ganciclovir and foscarnet has also been used but is associated with poor tolerability and a decrease in the quality of life. It appears that prompt initiation of treatment, before irreversible nerve necrosis occurs, results in a favorable outcome. Treatment often results in neurologic stabilization followed by improvement throughout a number of weeks. Treatment of HIV-associated progressive polyradiculopathy attributable to other causes is directed at the specific cause (eg, antimycobacterials for tuberculosis, intravenous penicillin for syphilis, and chemotherapy for lymphoma-related disease).

PN ASSOCIATED WITH IMMUNE RECONSTITUTION

HAART has been associated with numerous immune reconstitution illnesses, which generally occur within 6 months after its introduction and are thought to constitute an aberrant immune response to opportunistic pathogens.[64-67] Makela et al[68] described the occurrence of a probable recurrent Guillain-Barré syndrome 6 weeks after initiation of HAART and after a striking increase in CD4 cell count in 1 HIV-infected individual. Piliero et al[69] described an HIV-infected patient with AIDS who developed Guillain-Barré syndrome as early as 26 days after initiation of a 6-drug HAART regimen, which had led to an impressive immune reconstitution (a rise in CD4 cell count from 31 to 602 cells/μL). Although an immune-mediated inflammatory response to the peripheral nervous system may have been the cause of a rapidly progressive motor neuropathy in this patient, it is unclear how and why such a response occurred. Overall, it appears that immune reconstitution is only rarely associated with PNs in HIV-1–infected individuals.

CONCLUSION

Peripheral neuropathy is the most frequent neurologic complication of HIV infection or its treatment. The spectrum and the frequency of this complication are expected to change with continued experience and introduction of new antiretroviral drugs, an aging HIV-infected population, and the emergence of other long-term complications of HIV and/or its treatment. There is a great need for an improved understanding of these complications and their pathogenetic mechanisms as well as for the development of effective therapies that provide adequate symptomatic relief and halt or reverse the damage to the nerves.

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