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ABSTRACT: Neuromuscular disorders are common in human immunodeficiency virus (HIV); they occur at all stages of disease and affect all parts of the peripheral nervous system. These disorders have diverse etiologies including HIV itself, immune suppression and dysregulation, comorbid illnesses and infections, and side effects of medications. In this article, we review the following HIV-associated conditions: distal symmetric polyneuropathy; inflammatory demyelinating polyneuropathy; mononeuropathy; mononeuropathy multiplex; autonomic neuropathy; progressive polyradiculopathy due to cytomegalovirus; herpes zoster; myopathy; and other, rarer disorders. *Muscle Nerve* **40:** 1043–1053, 2009

NEUROMUSCULAR DISEASES ASSOCIATED WITH HIV-1 INFECTION

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There have been significant changes in the human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) epidemic since the original publication of this monograph in 1994. In resource-rich environments, highly active anti-retroviral therapy (HAART) has led to improved longevity in patients living with HIV, and in many patients HIV has become one of a number of chronic illnesses. Some of the comorbid conditions now frequently seen in HIV patients are the same as those that affect the general population, such as hypertension, diabetes, and obesity. Others, like HIV-associated nephropathy, are consequences of long-term exposure to HIV. Unfortunately, either due to lack of access to care, treatment failure, or medication non-adherence, there are still patients with advanced AIDS who are at risk for the neurologic complications seen commonly in the pre-HAART era. Over the past decade there have also been significant demographic shifts in the epidemic. In the United States, African Americans, Hispanics, and women, often of lower socioeconomic status, account for a growing number of new infections, and the overall population of people living with HIV/AIDS is aging. The effects of HAART, comorbidities, aging, and racial, ethnic, and socioeconomic disparities add new complexity to HIV and its related conditions.

Neurologic disorders are common in HIV. They occur at all stages of the disease and at all levels of the neuraxis. The etiologies of these disorders are variable and include HIV itself, the resulting immunosuppression and dysregulation, other co-morbid illnesses and infections, and side effects of HAART and other medications. In this review the neuromuscular complications of HIV in the HAART-era are summarized.

DISTAL SYMMETRIC POLYNEUROPATHY

Distal symmetric polyneuropathy (DSP) is the most common neurologic complication of HIV. It is estimated that currently more than 50% of patients with advanced HIV have evidence of DSP on

Abbreviations: AIDP, acute inflammatory demyelinating polyneuropathy; AIDS, acquired immunodeficiency syndrome; ALC, acetyl-L-carnitine; CK, creatine kinase; CMV, cytomegalovirus; CSF, cerebrospinal fluid; DILS, diffuse lymphocytosis syndrome; DRG, dorsal root ganglia; DSP, distal symmetric polyneuropathy; d4T, stavudine; ddI, didanosine; ddC, zalcitabine; EBV, Epstein–Barr virus; EDX, electrodiagnostic; EMG, electromyography; FDA, Food and Drug Administration; GBS, Guillain–Barré syndrome; HAART, highly active anti-retroviral therapy; HANWS, HIV-associated neuromuscular weakness syndrome; HIV, human immunodeficiency virus; IDP, inflammatory demyelinating neuropathy; IRIS, immune reconstitution inflammatory syndrome; IVIg, intravenous immunoglobulin; MND, motor neuron disease; MRI, magnetic resonance imaging; NCS, nerve conduction study; PCR, polymerase chain reaction; QST, quantitative sensory testing; RANTES, regulated-on-activation normal T-cell expressed and secreted (protein); SNAP, sensory nerve action potential; TB, tuberculosis; TNF-α tumor necrosis factor-alpha; VZV, varicella zoster virus

Key words: HIV; myopathy; neuromuscular; neuropathy; polyneuropathy

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neurologic examination.[1] Of these, many are symptomatic with numbness, pain, or paresthesias.[2] Although DSP usually occurs as a consequence of HIV, toxic neuropathy due to the anti-retrovirals stavudine (d4T), didanosine (ddI), and zalcitabine (ddC), commonly referred to as d-drugs, is clinically indistinguishable. These agents, which are thought to cause neuropathy via mitochondrial toxicity, are now uncommonly used in resource-rich environments, although they are still in use in the developing world.

Early studies recognized markers of advanced HIV infection, such as low CD4 count and high viral load, as well as exposure to d-drugs, as predictors of DSP.[3,4] Since the introduction of HAART, these risk factors have not been consistently reproduced. Some HAART-era studies have shown no increased risk of HIV-DSP in patients receiving d-drugs, but others have found demographic factors, including older age, male gender, and white race, to be associated with increased risk of HIV-DSP.[1,5,6] It is logical that comorbid conditions, such as diabetes mellitus, alcohol abuse, vitamin B_{12} deficiency, poor nutritional status, and perhaps hepatitis C, would also increase the risk of DSP, although this has not been proven.

The clinical presentation of HIV-associated DSP is similar to other forms of DSP, such as that seen in association with diabetes. Symptoms are usually symmetric and predominantly distal and sensory. Patients may experience numbness, tightness, pain, burning, or hyperalgesia in the feet. As the disease progresses, symptoms proceed proximally up the lower extremities and may ultimately involve the hands in a classic "stocking-and-glove" distribution. There is usually no clinically significant motor involvement, although weakness of the intrinsic muscles of the feet may be a feature of advanced disease. Physical examination reveals decreased distal vibratory and temperature sensation, with either decreased or hyperalgesic pinprick sensation in the toes. Proprioception and strength are often relatively preserved. Deep tendon reflexes are reduced at the ankles compared with the knees. Hyperactive knee reflexes are not uncommon and reflect the high prevalence of coexisting central nervous system disease in HIV.

Nerve conduction studies (NCSs) show abnormalities consistent with an axonal, distal, predominantly sensory polyneuropathy: reduction of sensory nerve action potential (SNAP) amplitudes; mild and symmetric reduction of conduction velocities; or mildly increased F-wave or H-reflex latencies.[7] Electromyography (EMG) abnormalities are usually minimal, but there may be abnormal spontaneous activity and motor unit potential changes consistent with distal denervation and reinnervation.[8]

The main pathologic studies of peripheral nerve in HIV were performed in the late 1980s and early 1990s. The studies were performed on biopsy and autopsy specimens taken almost exclusively from white men and included multiple types of neuropathy (DSP, inflammatory demyelinating polyneuropathy [IDP], mononeuropathy), as well as patients without neuropathy or lacking clinical data. The results were variable, showing both axonal (Fig. 1) and demyelinating (Fig. 2) features. Inflammation was reported inconsistently and, when present, it was macrophagic or lymphocytic.[9–13] Correlation with clinical signs and symptoms was also inconsistent. Some autopsy studies noted sural nerve abnormalities in patients with no history of DSP.[10,13] The detailed peripheral nerve pathology of HIV-associated DSP in a diverse, HAART-era population, along with its clinical correlates, has not been studied. There has been greater focus on skin biopsy. Intraepidermal nerve fiber density in distal lower extremity skin biopsy specimens is correlated with the clinical and electrophysiologic severity of HIV-associated DSP.[14] However, one study showed reduced intraepidermal nerve fiber density in less than half of patients with clinical signs consistent with DSP.[15] It is unclear whether this finding indicates variability in the pathology of HIV-associated DSP or is a reflection of imperfections inherent in the technique.

The pathogenesis of HIV-associated DSP is incompletely understood, but it is likely immune-mediated. HIV-infected activated macrophages have been demonstrated in dorsal root ganglia (DRG) from patients with HIV-DSP.[16] Supernatants from HIV-infected macrophages induce neuritic retraction in DRG culture, suggesting that activated macrophages may secrete neurotoxic mediators.[17] There has also been significant interest in the role of the HIV envelope protein, gp120. Early in vitro work recognized the ability of gp120 to bind to epitopes on peripheral nerve.[18] In animal studies, gp120 was able to bind to DRG neurons.[19] These findings led to the development of animal and in vitro models using gp120-induced neurotoxicity. In one such model, binding of gp120 to a chemokine receptor (CXCR4) on the Schwann cell membrane in DRG culture results in the release of the chemokine RANTES (regulated-on-activation normal T-cell expressed and secreted). RANTES then binds to the CCR5 receptor on the sensory neuron

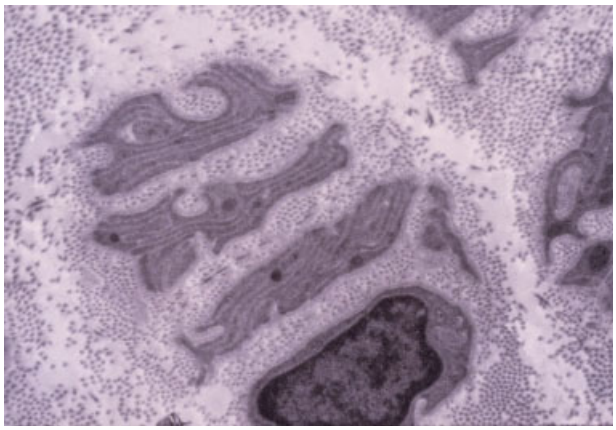

FIGURE 1. Electron micrograph of peripheral nerve in HIV-associated distal symmetric polyneuropathy demonstrates axonal loss with collapsed profiles of residual Schwann cells, which are devoid of axons (bands of Bungner). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

membrane, which leads to its apoptosis via tumor necrosis factor-alpha (TNF-α).[20] In later work, a compartmentalized DRG culture system was used to separately test the DRG cell and its axon. This model led to the hypothesis that gp120 may cause toxicity at the DRG and the peripheral axon through two independent mechanisms. In this model, the mechanism responsible for the direct gp120 toxicity to the axon is caspase-dependent.[21] In a rodent model, exposure of the sciatic nerve to gp120 results in decreased intraepidermal nerve fiber density in the hind paw, macrophage infiltration in the nerve and the DRG, and activated microglia in the dorsal horn of the spinal cord.[22]

Due to its high prevalence, DSP presenting with typical signs and symptoms in an HIV-positive patient does not require an extensive diagnostic evaluation. It is prudent to inquire after alcohol consumption and to perform simple blood tests to exclude glucose intolerance or diabetes and vitamin B_{12} deficiency. Nerve conduction studies and EMG may be helpful to confirm the diagnosis and document severity. Additional diagnostic studies, done in atypical cases or as part of research protocols, may include skin biopsy and quantitative sensory testing (QST). Nerve biopsy is indicated only in unusual cases.

There is currently no Food and Drug Administration (FDA)-approved treatment for HIV-associated DSP or its painful symptoms. Comorbid factors, such as diabetes or alcohol abuse, should be modified if possible. If the patient is taking neurotoxic medications that can safely be stopped or changed, it may be helpful to do so. In addition to the anti-retrovirals mentioned earlier, the following potentially neurotoxic medications are used for HIV-related conditions: chloramphenicol, dapsone, ethambutol, etoposide, isoniazid, metronidazole, pyridoxine, thalidomide, and vincristine.[23] As in other forms of neuropathy, clinical trials of potentially neuroregenerative therapies in HIV-associated DSP have been disappointing. Recombinant human nerve growth factor[24] and prosaptide,[25] agents that were neurotrophic in vitro and in animal models, were not effective in humans. Peptide T, an in vitro inhibitor of gp120 binding, also failed to show efficacy.[26] Acetyl-L-carnitine (ALC), a mitochondrial transport molecule, has been studied for the treatment of toxic neuropathy due to anti-retrovirals.[27,28] Results were mixed, but because ALC is generally safe and well tolerated many clinicians choose to use it.

Treatment of HIV-associated DSP is currently focused on management of neuropathic pain. Treatment recommendations are based on studies performed specifically in HIV-associated DSP, but also by inference from the diabetic neuropathy and post-herpetic neuralgia findings. Five main classes of agents are used: anticonvulsants; antidepressants; nonspecific analgesics; topical treatments; and alternative therapies. Among the anticonvulsants, gabapentin and lamotrigine have shown some efficacy in clinical trials in painful HIV-associated DSP.[29,30] Pregabalin is also

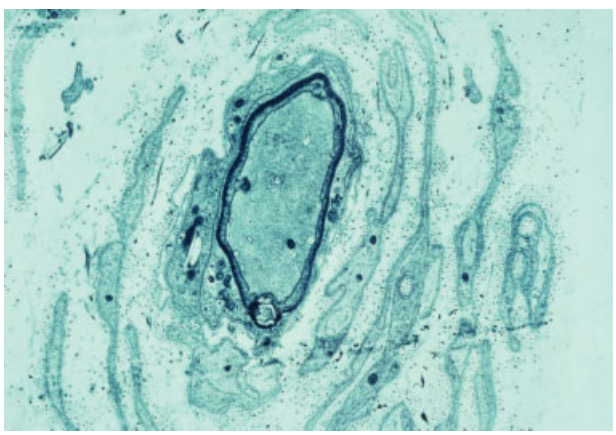

FIGURE 2. Electron micrograph of peripheral nerve in HIV-associated chronic inflammatory demyelinating polyneuropathy (CIDP) reveals onion-bulb formation, with a central large-caliber, thinly myelinated axon, surrounded by concentric whorls of Schwann cells. These changes are indicative of chronic bouts of demyelination and remyelination, characteristic of CIDP. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

commonly used based on its efficacy in diabetic neuropathy,[31,32] despite negative results in a recent clinical trial in HIV.[33] Among the antidepressants, amitriptyline has been studied specifically in HIV-associated DSP but failed to show efficacy.[34] Duloxetine is commonly used off-label in HIV based on findings in diabetic neuropathy, and studies in HIV are being planned.[35,36] A topical patch containing high-dose capsaicin has shown efficacy in HIV-associated DSP, and further trials are underway.[37] Topical application of aspirin/diethyl ether was effective in a small, randomized, double-blind, crossover, placebo-controlled study.[38] The lidocaine patch failed to show superiority to placebo but is nonetheless commonly used.[39] Alternative therapies include hypnosis[40] and smoked cannabis,[41] which have both shown efficacy in clinical trials but, for reasons of access for the former and regulatory concerns for the latter, are not typically recommended in clinical practice. Acupuncture was not efficacious in a controlled clinical trial.[34] Nonsteroidal anti-inflammatory drugs and acetaminophen are typically ineffective in the management of neuropathic pain. Opioids may be appropriate for moderate to severe neuropathic pain, but their use in the HIV-positive population is complicated. Patients who receive opioids for pain and have a personal or family history of substance abuse, a personal history of pre-adolescent sexual abuse, or psychiatric illness of any kind are at increased risk for developing a substance use disorder.[42] These factors are highly prevalent in the HIV-positive population and, although they do not preclude the use of opiates, they require the clinician to exercise particular caution. A multidisciplinary approach, involving neurologists, pain specialists, psychiatrists, and infectious disease clinicians, may be most effective.

OTHER NEUROPATHIES

Although DSP is clearly the most common peripheral nerve disorder seen in patients with HIV, other neuropathic conditions also occur, such as polyradiculopathy, acute and chronic inflammatory demyelinating polyneuropathies (IDPs), mononeuropathies, mononeuropathy multiplex, and autonomic neuropathy. Three factors specific to HIV make the diagnosis of these disorders of particular interest. First, the high prevalence of DSP in the HIV population makes the coexistence of more than one neuropathic condition in the same patient a distinct possibility, and it may complicate both the clinical picture and electrodiagnostic (EDX) study. Second, the underlying etiologies of these neuropathies vary based on the immune status of the patient. For example, inflammatory neuropathies usually occur at higher CD4 counts, whereas neuropathies due to opportunistic infections such as cytomegalovirus (CMV) are prominent at lower CD4 counts. Third, other infectious agents, such as syphilis, varicella zoster virus (VZV), and tuberculosis (TB), more commonly affect persons with HIV and may have neurologic sequelae. In our clinical and EDX practice, these complexities have at times led to neuropathic syndromes that did not fit neatly into one of the diagnostic categories just listed, and there is likely significant overlap between the syndromes.[43] They nonetheless provide a useful framework. The history of progression of symptoms, the neurologic examination, and ancillary diagnostic studies, such as NCSs and EMG, neuroimaging, and cerebrospinal fluid (CSF) analysis, are often helpful for diagnosis in these disorders.

Inflammatory Demyelinating Polyneuropathy. IDP may occur in its acute form (AIDP) or Guillain–Barré syndrome (GBS), early in the course of disease as part of the acute retroviral syndrome.[44] In this setting, its manifestations are similar to those seen in HIV-negative patients with AIDP and, due to the absence of data specific to HIV, treatment recommendations are derived from experience in HIV-negative patients. Most patients presenting with AIDP are initially managed in an inpatient setting to begin treatment and monitor for dangerous complications such as autonomic instability and respiratory failure. First-line treatment of AIDP is either plasmapheresis or intravenous immunoglobulin (IVIg).[45]

In our experience, the chronic form, CIDP, is more common than AIDP in HIV. HIV-positive patients, especially those with a high CD4 count, may present similarly to their HIV-negative counterparts, with relapsing motor and sensory symptoms that require ongoing immunomodulatory treatment. However, atypical phenotypes are not uncommon. Three patients have been observed who presented with monophasic, slowly progressive, multifocal, lower extremity symptoms associated with demyelination on NCSs, and one had a Lewis–Sumner-like syndrome with exclusively upper extremity signs and symptoms. In all four patients these abnormalities resolved after a single course of IVIg and have not recurred. Such cases may fall into the overlap between

mononeuropathy multiplex and IDP, as described by some investigators.[8,43]

Diagnostic evaluation for IDP typically includes magnetic resonance imaging (MRI) of the relevant spinal segments, with and without gadolinium, to exclude a mass lesion or infiltrative process in the nerve roots. MRI may be normal or reveal nerve root enhancement. NCSs show features of demyelination such as slowing of conduction velocity, temporal dispersion, conduction block, and prolonged distal latencies and late responses.[44] CSF analysis is usually performed, but it may be nondiagnostic in patients with high CD4 counts. This is because the CSF of asymptomatic HIV patients may show a mild lymphocytic pleocytosis and elevated protein, thus obscuring the abnormalities typically associated with CIDP (elevated protein without pleocytosis). CSF analysis is more important in patients with CD4 counts below 200 in whom the suspicion of an underlying infectious or malignant etiology is higher. This will be addressed in what follows in the discussion of polyradiculopathy, because the differential diagnosis is similar.

Treatment options for CIDP in HIV are derived from the HIV-negative literature, with a few common-sense caveats. Although corticosteroids should not be withheld from HIV-positive patients if necessary, extra thought should be given to the potential for side effects, including immunosuppression, metabolic derangement, and osteoporosis. If available, IVIg may be a better option.

Mononeuropathies. Mononeuropathies are relatively common in patients with HIV infection. This is in part due to the high prevalence of common entrapment neuropathies, such as median neuropathy at the wrist and ulnar neuropathy at the elbow, in the general population. It is also logical to presume that HIV may have a deleterious effect on peripheral nerve that may predispose patients to entrapment neuropathies even in the absence of an observable polyneuropathy, although this is unproven. In general, these focal neuropathies are treated no differently than they are in the HIV-negative population. Focal cranial neuropathies warrant special mention. Unilateral and bilateral facial palsies may occur in HIV-positive patients. The following discussion is confined to facial palsy occurring in isolation or in the context of other cranial neuropathies, although it may occur as part of a more extensive neuropathic process such as IDP or mononeuropathy multiplex.

Facial palsies have been described in the context of seroconversion with aseptic HIV-associated meningitis, but they can occur at any stage of disease.[46] In most cases, a specific etiology cannot be found, and the facial palsy is classified as idiopathic or Bell's palsy. Specific etiologies of facial palsies in HIV reported in the literature include the VZV and meningeal lymphomatosis.[47] Syphilis and TB are other potential causes.[48] All of these etiologies have the potential to cause multiple cranial neuropathies. VZV typically causes a facial palsy as part of the Ramsay Hunt syndrome, which is caused by reactivation of latent VZV in the geniculate ganglion causing a polyneuritis that may involve cranial nerves V, VII, VIII, and IX. Ramsay Hunt syndrome is characterized by a herpetic eruption in the cutaneous distribution of the trigeminal nerve accompanied by facial nerve palsy and ear pain.[49] Other symptoms may include tinnitus, vertigo, and loss of hearing or taste. Ramsay Hunt syndrome in the general population is typically treated with antivirals and corticosteroids, although a recent Cochrane review found insufficient evidence to recommend these treatments.[50,51] Despite the lack of evidence specific to Ramsay Hunt syndrome, some have justified this approach in light of the more complete data available for treatment of herpes zoster in other parts of the body.[52] This is addressed in greater detail in the discussion of polyradiculopathies. In the HIV-positive patient with Ramsay Hunt syndrome, antiviral treatment seems prudent. The potential risks and benefits of adjunctive corticosteroids must be weighed for each individual patient, taking into account the degree of immunocompromise.

TB can lead to cranial neuropathies by causing a basilar meningitis. We also observed a painful abducens nerve palsy in a patient with confirmed pulmonary TB, which resolved with anti-tubercular treatment.

In general, Bell's palsy has been attributed to vascular, inflammatory, and viral etiologies, especially herpes viruses. This has led to the common practice of empiric treatment with corticosteroids and antivirals such as acyclovir. Recently, data from a large clinical trial indicated that in the general population corticosteroids are effective in the treatment of Bell's palsy, but antivirals are not.[53] The implication of these findings for the HIV-positive population is unclear. Clinicians may choose to treat these patients with antivirals anyway with the rationale that herpes viruses are often more active in HIV, and therefore they are more likely to be the cause of the Bell's palsy.

Mononeuropathy Multiplex. Classic mononeuropathy multiplex, with painful, stepwise, multifocal deficits due to nerve infarction associated with vasculitis, appears to be rare in HIV. This dramatic syndrome has been clinically and pathologically well described in the early literature in patients with advanced AIDS and CMV infection.[54] In these patients mononeuropathy multiplex may be rapidly progressive; it quickly involves multiple nerve distributions and even becomes confluent. Decreased motor and sensory potentials consistent with axonal degeneration are most often seen on nerve conduction studies.[55]

Electromyography may show denervation. A positive CMV polymerase chain reaction in CSF, evidence of CMV on nerve biopsy (Fig. 3), or evidence of CMV infection in other organs, such as retinitis, pneumonia, and gastroenteritis, may be helpful in diagnosis, but the clinician may choose to treat empirically even in the absence of clearly demonstrable CMV. Treatment is done with antivirals such as ganciclovir, foscarnet, and cidofovir. In addition, immune reconstitution with HAART should be attempted whenever possible. The prognosis for recovery is poor, which is at least in part due to the overall health status of these patients. A milder form of mononeuropathy multiplex, involving one or a few nerves, occurs in HIV patients with high CD4 counts. This syndrome is probably immune-mediated and may be a variant of IDP with more prominent axonal features.[43] Deficits are most often self-limited, resolving after several months.[56,57] Immunomodulatory treatment, such as corticosteroids, plasmapheresis, or IVIg, may provide benefit in patients with inadequate spontaneous recovery.[58] Due to the high rate of co-infection with hepatitis C, vasculitis associated with cryoglobulinemia should also be considered in the differential diagnosis of mononeuropathy multiplex in HIV-positive patients.[59]

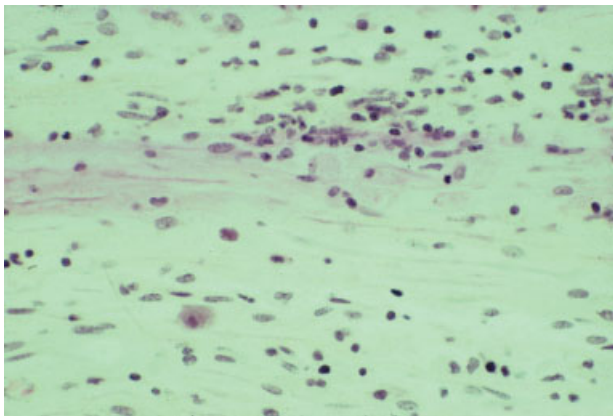

FIGURE 3. Hematoxylin–eosin (H&E)-stained section of peripheral nerve from an AIDS patient with progressive weakness and sensory loss reveals an endoneurial inflammatory infiltrate. An enlarged cell with a nuclear inclusion characteristic of cytomegalovirus appears in a cell in the lower left quadrant of the image. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Autonomic Neuropathy. Autonomic neuropathy is common in other systemic conditions associated with high rates of DSP, such as diabetes. Early reports from the pre-HAART era suggested that autonomic neuropathy was also common in HIV-positive patients,[60,61] but these results have not been consistently reproduced in the HAART era.[62,63] There are several studies from the cardiac literature that demonstrate cardiac autonomic dysfunction in HIV as reflected by decreased heart rate variability.[64,65] A study from India assessing the autonomic nervous system in the context of the hypothalamic–pituitary–adrenal axis also demonstrated attenuated autonomic function.[66] However, two recent studies, performed in Mozambique[62] and India,[63] respectively, failed to demonstrate objective autonomic abnormalities using a standard battery of autonomic testing. The study from Africa found more autonomic symptoms in HIV-positive patients. Further research is needed to determine the prevalence and impact of autonomic neuropathy in HIV.

Radiculopathies. ***Progressive Polyradiculopathy.*** CMV can infect the cauda equina and lead to inflammation and necrosis of the lumbosacral nerve roots and a progressive polyradiculopathy in patients with advanced AIDS.[67] Patients present with a rapidly evolving cauda equina syndrome, including weakness and numbness in the lower extremities and sphincter dysfunction. Neurologic examination reveals a flaccid paraparesis and lower extremity areflexia. The upper extremities and cranial nerves may be involved in advanced cases. Management and prognosis is similar to that described earlier for CMV-related mononeuropathy multiplex. Although rarer, a similar clinical picture can be caused by neurosyphilis or lymphomatous meningitis.[68,69] In addition, we recently observed a patient with a CD4 count above 200 who presented with asymmetric weakness of the lower extremities that progressed over 1 year. Nerve root biopsy revealed Epstein–Barr virus (EBV)-associated neurolymphomatosis of the cauda equina.

Gadolinium-enhanced MRI of the lumbosacral spine is usually the first diagnostic step and is necessary to exclude compressive lesions in patients with

suspected progressive polyradiculopathy. The study may be normal, or it may show meningeal enhancement in the cauda equina.[70] Lumbar puncture is also essential, as the diagnosis of CMV-related polyradiculitis is confirmed by detection of CMV in CSF with polymerase chain reaction (PCR). Low glucose, elevated protein, and a prominent polymorphonuclear pleocytosis are considered classical findings, but a relatively normal CSF does not exclude the diagnosis.[71,72] EDX studies show evidence of severe axonal polyradiculopathy, including low-amplitude or absent responses with nerve conduction studies and extensive denervation of lower extremity muscles on needle EMG.[67,73]

Herpes Zoster. Although not specific to the HIV population, VZV deserves mention in the discussion of polyradiculitis. Typically acquired in childhood, VZV remains dormant in the DRG of the immunocompetent host. The reactivation of VZV as herpes zoster or shingles occurs with much greater frequency in the HIV-positive population and may occur at any CD4 count.[74] Herpes zoster is characterized by pain and itching followed by a vesicular rash in a dermatomal distribution. The trigeminal nerve distribution and the thoracic dermatomes are affected most commonly, although any dermatome may be involved. Occasionally, VZV may reactivate with painful symptoms but without a rash, a condition called zoster *sine herpete*. Treatment with acyclovir speeds recovery of herpes zoster in HIV-positive patients.[74] Treatment with corticosteroids accelerates healing and reduces acute pain in the general population, but it does not reduce the incidence of post-herpetic neuralgia, a chronic pain syndrome that may develop in the same distribution as the herpes zoster.[75,76] Data specific to HIV-positive patients are not available. The risk–benefit ratio of corticosteroids should be weighed for each patient based on their immune status and comorbid conditions. Post-herpetic neuralgia is difficult to treat. Treatment with anticonvulsants, tricyclics and other antidepressants, and topical preparations may be helpful.[77] The VZV vaccine currently used to prevent herpes zoster in older adults is a live attenuated virus and is contraindicated in immunocompromised patients, according to its prescribing information. The role of the vaccine in HIV patients with high CD4 counts requires further study.

MYOPATHY

Several disorders of muscle have been reported in patients with HIV. These disorders range in severity from myalgias and asymptomatic elevation of creatine kinase (CK) to rhabdomyolysis. These muscle disorders are rare. HIV-associated myopathy, also known as HIV-associated polymyositis, is the most common. It is clinically and pathologically similar to autoimmune polymyositis in HIV-negative patients. It occurs at all stages of HIV disease, and it is characterized by slowly progressive, proximal, and symmetric weakness.[78] Myalgias are often present but are not specific. The classic diagnostic criteria used to define polymyositis in HIV-negative patients are useful in the diagnosis of HIV-associated myopathy. These include objective muscle weakness, elevated serum CK, myopathic findings on EMG, and a myopathic muscle biopsy (Fig. 4).[79] Pathologic characteristics include inflammatory infiltrates of $CD8^+$ T cells and macrophages surrounding major histocompatibility complec (MHC)-I–expressing muscle fibers, primarily in the endomysial parenchyma. Fiber necrosis may also be seen.[80] The role of serum antibodies associated with polymyositis in the general population, such as anti–Jo-1, is unclear in HIV-associated myopathy.

Due to the rarity of HIV-associated myopathy, the prognosis and best course of treatment are not well established. The largest case series ($n = 13$) indicated that over half of those treated with corticosteroids attained complete remission and were able to discontinue therapy after a mean of 9 months.[81] The remainder of the patients improved over months to years. Our experience has been more variable. Although several of our patients have responded to immunomodulatory therapy

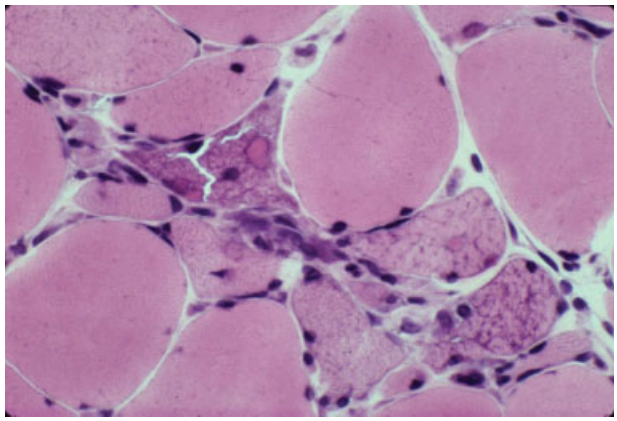

FIGURE 4. H&E section of muscle from an HIV patient with proximal weakness reveals degenerating, basophilic myofibers, several of which contain dark pink cytoplasmic bodies. These changes are characteristic of HIV-associated myopathy. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

with corticosteroids or IVIg, we follow several patients with HIV-associated myopathy who have had significant weakness for many years with only modest response to these treatments. Other immunosuppressive therapies that are used in the treatment of polymyositis, such as methotrexate and azathioprine, may be considered in HIV-associated myopathy, but there is little evidence of their efficacy, and immunosuppressant toxicity is a concern.[81] The mechanism by which HIV leads to inflammatory myopathy is not fully understood, but a T-cell–mediated and MHC I–restricted cytotoxic process triggered by HIV has been proposed.[80] HIV-associated myopathy has also been described as part of an immune reconstitution inflammatory syndrome (IRIS).[82]

Certain anti-retrovirals may lead to toxic myopathy, presumably through impairment of mitochondrial function.[83] Zidovudine (AZT) myopathy can manifest as fixed weakness or exercise intolerance, which resolves within months of withdrawing the drug. The CK level is normal or mildly elevated, and muscle biopsy reveals ragged red fibers.[84] Stavudine (d4T), which is now used uncommonly in resource-rich nations, can cause HIV-associated neuromuscular weakness syndrome (HANWS).[85] HANWS is characterized by rapidly progressive weakness, resembling GBS, associated with lactic acidosis, nausea, vomiting, weight loss, abdominal distension, hepatomegaly, and lipoatrophy. EDX studies and pathologic specimens, reported in a study of 69 patients, revealed heterogeneous etiologies of weakness. Severe axonal polyneuropathy was the most common; demyelinating and mixed neuropathies and myopathy occurred as well. Muscle biopsy specimens revealed evidence of mitochondrial dysfunction, including ragged red fibers and depletion of mitochondrial DNA.[85] These findings, together with lactic acidosis, support a mitochondrial mechanism.

There are reports of various other forms of myopathy in HIV-positive patients. Infectious myopathy, or pyomyositis, has been described in patients with advanced AIDS. Infections are usually bacterial with *Staphylococcus aureus* cultured most commonly.[86] Other possible causative organisms include toxoplasmosis,[87] cryptococcus,[88,89] and *Mycobacterium avium intracellulare*.[89] The wasting syndrome seen in AIDS may be a myopathy in some cases.[90] Acute rhabdomyolysis with myalgia, weakness, and markedly elevated CK level has been reported either as an effect of HIV itself or as a side effect of medications including didanosine.[91] Dermatomyositis,[92] nemaline rod myopathy,[93] and inclusion-body myositis[94] have also been reported.

OTHER NEUROMUSCULAR DISEASES

Diffuse infiltrative lymphocytosis syndrome (DILS) is a rare condition in which HIV triggers a systemic CD8 lymphocytosis, resulting in a Sjögren-like syndrome.[95] The neuromuscular complications of DILS are peripheral neuropathy[96] and, less frequently, inflammatory myopathy.[81] The prevalence of DILS has decreased markedly in the HAART era.[95]

There are multiple reports of various types of motor neuron disease (MND) in HIV-positive patients, including primary lateral sclerosis, brachial amyotrophic diplegia, pseudobulbar syndrome, as well as classic amyotrophic lateral sclerosis (ALS).[97–100] Several differences between these patients and their HIV-negative counterparts have been described, such as younger age, more rapidly progressive course, and response to anti-retroviral therapy. It is currently unclear if there is a true association between MND and HIV.[100]

Myasthenia gravis has been reported in the course of HIV infection, but a causal relationship has not been shown.[101] A sensory neuronopathy has been described in several patients.[102] Neuromuscular complications of West Nile virus, including an acute flaccid monoparesis and an acute flaccid paraplegia, have been reported in HIV-positive patients, but the significance of this association is unclear.[103,104]

In conclusion, neuromuscular disorders may develop at any stage of HIV. As HAART has turned HIV into a chronic illness, its neuromuscular complications have changed. However these disorders, especially DSP, are still prevalent and continue to impair quality of life.

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