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Neuromuscular Diseases Associated with HIV-1 Infection

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Abstract

Neuromuscular disorders are common in HIV, occurring at all stages of disease and affecting all parts of the peripheral nervous system. These disorders have diverse etiologies including HIV itself, immune suppression and dysregulation, co-morbid 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.

Keywords

HIV; neuropathy; polyneuropathy; myopathy; neuromuscular

Introduction

Since the original publication of this minimonograph in 1994, there have been significant changes in the HIV/AIDS epidemic. In resource-rich environments, highly active anti-retroviral therapy (HAART) has led to improved longevity in patients living with HIV. In many patients, HIV has become one of a number of chronic illnesses. Some of the co-morbid 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 U.S., 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, co-morbidities, 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 disease and at all levels of the neuraxis. The etiologies of these disorders are variable and include HIV itself and the resulting immunosuppression and dysregulation; other co-morbid illnesses and infections; and side effects of HAART and other medications. In this review we will summarize the neuromuscular complications of HIV in the HAART-era.

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 neurologic examination.¹ Of these, many are symptomatic with numbness, pain or paresthesias.² Although DSP usually occurs as a consequence of HIV itself, toxic neuropathy due to the antiretrovirals 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} However 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, 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 co-morbid conditions such as diabetes mellitus, alcohol abuse, vitamin B12 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 as compared to the knees. Hyperactive knee reflexes are not uncommon and reflect the high prevalence of co-existing central nervous system disease in HIV.

Nerve conduction studies (NCS) 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 may reveal spontaneous activity and motor unit changes consistent with distal denervation and reinnervation.⁸

The main pathological studies of peripheral nerve in HIV were performed in the late 1980s and early 1990s. The studies were performed on biopsy and autopsy specimens almost exclusively from white men and included multiple types of neuropathy (DSP, IDP, mononeuropathy), as well as patients with no neuropathy, or without clinical data. The results were variable, showing both axonal (figure 1) and demyelinating (figure 2) features. Inflammation was reported inconsistently, and when present, was macrophagic or lymphocytic.^{9–13} Correlation with clinical signs and symptoms was also inconsistent, with some autopsy studies noting sural nerve abnormalities in patient without histories 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 is likely immune-mediated. HIV-infected activated macrophages have been demonstrated in dorsal root ganglia (DRG) from patients with HIV-DSP¹⁶, and supernatants from HIV-infected macrophages induce neuritic retraction in DRG culture, suggesting that activated macrophages may secrete neurotoxic mediators¹⁷. 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 present 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. RANTES then binds to the CCR5 receptor on the sensory neuron membrane, which leads to its apoptosis via TNF- α .²⁰ In later work, a compartmentalized DRG culture system was used to separately test the dorsal root ganglion 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. Inquiring after alcohol consumption and simple blood tests to exclude glucose intolerance or diabetes and vitamin B12 deficiency are prudent. 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 FDA-approved treatment for HIV-associated DSP or its painful symptoms. Co-morbid factors, such as diabetes or alcohol abuse, should be modified as possible. If the patient is taking neurotoxic medications which can safely be stopped or changed, it may be helpful to do so. As in other forms of neuropathy, clinical trials of potentially neuroregenerative therapies in HIV-associated DSP have been disappointing. Recombinant human nerve growth factor²³ and prosaptide²⁴, agents which were neurotrophic *in vitro* and in animal models, were not in humans. Peptide T, an *in vitro* inhibitor of gp-120 binding, also failed to show efficacy.²⁵

Treatment of HIV-associated DSP is currently focused on management of neuropathic pain. Treatment recommendations are based on studies done specifically in HIV-associated DSP but also by inference from the diabetic neuropathy and post-herpetic neuralgia literatures. 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.^{26, 27} Pregabalin is also commonly used based on its efficacy in diabetic neuropathy^{28, 29} despite the negative results of a recent clinical trial in HIV.³⁰ Among the antidepressants amitriptyline has been studied specifically in HIV-associated DSP but failed to show efficacy.³¹ Duloxetine is commonly used off label in HIV based on the literature in

diabetic neuropathy, and studies in HIV are being planned.^{32, 33} A topical patch containing high dose capsaicin has shown efficacy in HIV-associated DSP and further trials are underway.³⁴ The lidocaine patch failed to show superiority to placebo but is nonetheless commonly used.³⁵ Alternative therapies include hypnosis³⁶ and smoked cannabis³⁷ 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.³¹ 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 preadolescent sexual abuse, or psychiatric illness of any kind are at increased risk for developing a substance use disorder.³⁸ These factors are highly prevalent in the HIV-positive population and while they do not preclude the use of opiates, they require the clinician to exercise particular caution. A multi-disciplinary 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 such as polyradiculopathy, acute and chronic inflammatory demyelinating polyneuropathies (IDP), mononeuropathies, mononeuropathy multiplex and autonomic neuropathy also occur. Three factors specific to HIV make the diagnosis of these disorders particularly interesting. 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 may complicate both the clinical picture and the electrodiagnostic studies. 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 while neuropathies due to opportunistic infections such as cytomegalovirus (CMV) are important at lower CD4 counts. Third, other infectious agents such as syphilis, varicella zoster virus (VZV), and tuberculosis more commonly affect persons with HIV and may have neurologic sequelae. In our clinical and electrodiagnostic practice, these complexities have at times led to neuropathic syndromes that did not fit neatly into one of the diagnostic categories listed above, and there is likely significant overlap between the syndromes.³⁹ They nonetheless provide a useful framework. In these disorders the history of progression of symptoms, the neurologic examination, and ancillary diagnostic studies such as NCS and EMG, neuroimaging and cerebrospinal fluid analysis are often helpful for diagnosis.

Inflammatory demyelinating polyneuropathy—Inflammatory demyelinating polyneuropathy (IDP) may occur in its acute form, AIDP or Guillain-Barre syndrome (GBS), early in the course of disease as part of the acute retroviral syndrome.⁴⁰ 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).⁴¹

In our experience, the chronic form, CIDP, is more common in HIV. HIV-positive patients, especially those with 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. We have observed three patients who presented with monophasic, slowly progressive, multifocal, lower extremity symptoms associated with demyelination on NCS, and one with a Lewis Sumner-like syndrome with exclusively upper extremity signs and symptoms. 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 described by some authors.^{8, 39}

Diagnostic evaluation for IDP typically includes 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. NCS show features of demyelination such as slowing of conduction velocity, temporal dispersion, conduction block, and prolonged distal latencies and late responses.⁴⁰ Cerebrospinal fluid (CSF) analysis is usually performed, but may be non-diagnostic in patients with high CD4 count. 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 count below 200 in whom the suspicion of an underlying infectious or malignant etiology is higher. This will be addressed further below 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 immune suppression, 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 the 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. 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 can occur at any stage of disease.⁴² In most cases a specific etiology cannot be found and so the facial palsy is classified as idiopathic or Bell's palsy. Specific etiologies of facial palsies in HIV reported in the literature include the varicella zoster virus (VZV) and meningeal lymphomatosis.⁴³ Syphilis and tuberculosis (TB) are other potential causes.⁴⁴ 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.⁴⁵ 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.^{46, 47} 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.⁴⁸ This will be addressed in greater detail as part of 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 have also observed a painful abducens nerve palsy in a patient with confirmed pulmonary TB which resolved with anti-tubercular treatment.

In the general population idiopathic facial palsy, or 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 have indicated that in the general population corticosteroids are effective in the treatment of Bell's palsy but antivirals are not.⁴⁹ 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 more likely to be causative 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 is clinically and pathologically well described in the early literature in patients with advanced AIDS and CMV infection.⁵⁰ In these patients mononeuropathy multiplex may be rapidly progressive, quickly involving multiple nerve distributions, and even becoming confluent. Decreased motor and sensory potentials consistent with axonal degeneration are most often seen on nerve conduction studies.⁵¹ Electromyography may show denervation. A positive CMV PCR in CSF, evidence of CMV on nerve biopsy (figure 3), or evidence of CMV infection in other organs such as retinitis, pneumonia, and gastroenteritis, is helpful in diagnosis, but the clinician may choose to treat empirically even in the absence of clearly demonstrable CMV. Treatment is 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+ count. This syndrome is probably immune mediated and may be a variant of IDP with more prominent axonal features.³⁹ Deficits are most often self-limited, resolving after several months.^{52, 53} However in patients with inadequate spontaneous recovery, immunomodulatory treatment such as corticosteroids, plasmapheresis, or IVIg may provide benefit.⁵⁴

Autonomic Neuropathy—In other systemic conditions associated with high rates of DSP, such as diabetes, autonomic neuropathy is also common. Early reports from the pre-HAART era suggested that autonomic neuropathy was also common in HIV positive patients,^{55, 56} but these results have not been consistently reproduced in the HAART-era.^{57, 58} There are several studies from the cardiac literature that demonstrate cardiac autonomic dysfunction in HIV as reflected by decreased heart rate variability.^{59, 60} An Indian study assessing the autonomic nervous system in the context of the hypothalamic-pituitary-adrenal axis also demonstrated attenuated autonomic function.⁶¹ However two recent studies, performed in India⁵⁸ and Mozambique⁵⁷, failed to demonstrate autonomic abnormalities using a standard battery of autonomic testing. The African study did find 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—In addition to causing mononeuropathy multiplex, in the patient with advanced AIDS, CMV can infect the cauda equina leading to inflammation and necrosis of the lumbosacral nerve roots and a progressive polyradiculopathy.⁶² Patients present with a rapidly evolving cauda equina syndrome, with weakness and numbness in the lower extremities and sphincter dysfunction. Neurological 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 above for CMV-related mononeuropathy multiplex. Although rarer, a similar clinical picture can be caused by neurosyphilis or lymphomatous meningitis.^{63, 64} In addition, we recently observed a patient with a CD4+ count of above 200 who presented with asymmetric weakness of the lower extremities that progressed over one year. Nerve root biopsy revealed EBV-associated neurolymphomatosis of the cauda equina.

Gadolinium enhanced MRI of the lumbosacral spine, is usually the first diagnostic step in patients with suspected progressive polyradiculopathy. Although the study may be normal, or show only meningeal enhancement in the cauda equina, it is necessary to exclude focal compressive lesions of the cauda equina.⁶⁵ Lumbar puncture is also essential, as the diagnosis of CMV-related polyradiculitis is confirmed by detection of CMV in CSF with the polymerase chain reaction (PCR). Low glucose, elevated protein, and a prominent polymorphonuclear pleocytosis in the CSF, are considered classical findings, but a relatively normal CSF does not exclude the diagnosis.^{66, 67} Electrodiagnostic 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.

Herpes zoster—Although not specific to the HIV population, varicella zoster virus (VZV) deserves mention in the discussion of polyradiculitis. Typically acquired in childhood, VZV remains dormant in the dorsal root ganglia 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.⁶⁹ 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 herpette. Treatment with acyclovir speeds recovery of herpes zoster in HIV-positive patients.⁶⁹ Treatment with corticosteroids accelerates healing and reduces acute pain in the general population,^{70, 71} but data specific to HIV-positive patients are not available. The risk-benefit of corticosteroids should be weighed for each patient based on their immune status and co-morbid conditions. Post-herpetic neuralgia, a chronic pain syndrome, may develop in the same distribution as the herpes zoster. Treatment with anticonvulsants, tricyclic antidepressants, and topical lidocaine preparations may be helpful.⁷² The VZV vaccine currently in use employs a live attenuated virus and is contraindicated in immunocompromised patients. The role of the vaccine in HIV patients with high CD4+ count requires further study.

Myopathy

Several disorders of muscle have been reported in patients with HIV. These disorders range in severity from myalgia and asymptotically elevated CK to rhabdomyolysis. Although these muscle disorders are all rare, the most common is HIV-associated myopathy, also known as HIV-associated polymyositis. HIV-associated myopathy is clinically and pathologically similar to autoimmune polymyositis in HIV-negative patients. It occurs at all stages of HIV disease, and is characterized by slowly progressive, proximal, and symmetric

weakness.⁷³ Myalgias are often present but are not specific. The diagnostic criteria used to define polymyositis in HIV-negative patients are also 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 (figure 4).⁷⁴ The presence of all four criteria leads to a definitive diagnosis; if three are met the diagnosis is probable. Pathologic characteristics include inflammatory infiltrates of T-cells and macrophages primarily in the endomysial parenchyma. Fiber necrosis may also be seen.⁷⁵

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) found that over half of those treated with corticosteroids attained complete remission and were able to discontinue therapy after a mean of 9 months.⁷⁶ The remainder of the patients improved over months to years. Our experience has been more variable. While several of our patients have responded to immunomodulatory therapy with corticosteroids or IVIg, we follow several patients with HIV-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 efficacy, and concern over their immunosuppressant toxicity.⁷⁶ 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.⁷⁵ HIV-associated myopathy has also been described as part of an immune reconstitution inflammatory syndrome (IRIS).⁷⁷

Certain antiretrovirals may lead to toxic myopathy, presumably through impairment of mitochondrial function.⁷⁸ Zidovudine (AZT) myopathy can manifest as fixed weakness or exercise intolerance which resolves within months of withdrawing the drug. CK level is normal or mildly elevated and muscle biopsy reveals ragged red fibers.⁷⁹ Stavudine (d4T), which is now used uncommonly in resource-rich nations, can cause HIV-associated neuromuscular weakness syndrome (HANWS).⁸⁰ HANWS is characterized by rapidly progressive weakness, resembling Guillain-Barre syndrome, associated with lactic acidosis, nausea, vomiting, weight loss, abdominal distension, hepatomegaly and lipoatrophy. Electrodiagnostic studies and pathologic specimens reported in a study of 69 patients, revealed heterogeneous etiologies of weakness. Severe axonal polyneuropathy was the most common, however demyelinating and mixed neuropathies as well as myopathy also occurred. Muscle biopsy specimens revealed evidence of mitochondrial dysfunction, including ragged red fibers and depletion of mitochondrial DNA.⁸⁰ 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 commonly⁸¹. Other possible causative organisms include: toxoplasmosis⁸², cryptococcus^{83,84} and mycoplasma avium intracellulare⁸⁴. The wasting syndrome seen in AIDS may be a myopathy in some cases.⁸⁵ 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.⁸⁶ Dermatomyositis⁸⁷, nemaline rod myopathy⁸⁸, and inclusion body myositis⁸⁹ 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 Sjogren-like syndrome.⁹⁰ The neuromuscular complications of DILS are peripheral neuropathy⁹¹ and more rarely

inflammatory myopathy.⁷⁶ The prevalence of DILS has markedly decreased in the HAART-era.⁹⁰ There are reports of motor neuron disease in HIV-positive patients associated with response to antiretroviral therapy.⁹² However it is unclear if there is a true association.⁹³ Similarly, myasthenia gravis has been reported in the course of HIV infection but a causal relationship has not been shown.⁹⁴ A sensory neuropathy has also been described in several patients.⁹⁵

Conclusion

Neuromuscular disorders may develop at any stage of HIV. As highly active anti-retroviral therapy (HAART) has turned HIV into a chronic illness, its neuromuscular complications have changed. However these disorders, especially distal symmetric polyneuropathy (DSP), are still prevalent and continue to impair quality of life.

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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).

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.

Figure 3. H & E 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 right lower quadrant of the image.

Figure 4. H & E section of muscle from an HIV patient with proximal weakness reveals degenerating, basophilic myofibers; several contain dark pink cytoplasmic bodies. These changes are characteristic of HIV-associated myopathy.