Peripheral nerve complications of HIV–1 infection

Historical note and nomenclature

Incidence. Neurologic complications of HIV–1 have been reported for over 20 years (Britton et al 1982; Miller et al 1982), and it is widely appreciated that the entire neuraxis is susceptible to complications. With the advent of HAART and prolonged survival, the incidence of most neurologic complications has declined; however, the incidence of distal sensory polyneuropathy has increased, with distal sensory polyneuropathy and antiretroviral toxic neuropathy remaining the most frequently reported neurologic manifestations. Other peripheral nerve complications include acute or chronic demyelinating neuropathies, mononeuritis or mononeuritis multiplex, autonomic neuropathy, and polyradiculopathy (Brew 2003).

In retrospective studies of patients with acquired immune deficiency syndrome, the incidence of peripheral neuropathy syndromes is estimated to be 10% (Snider et al 1983; Levy et al 1985). When including patients with electrophysiologic evidence of polyneuropathy who lack clinical symptoms of peripheral neuropathy, the incidence rises to 40% (Janssen et al 1988; So et al 1988). This figure increases to 48% to 100% in pathologic studies (de la Monte et al 1988; Mah et al 1988).

Prospective series reveal an incidence of peripheral neuropathy of 5% to 60%, depending on the disease stage and neuropathy definition (So et al 1988; Chavanet et al 1989; Hall et al 1991; Husstedt et al 1993; Bacellar et al 1994; Schifitto et al 2002; Ellis et al 2010). A study of 252 patients enrolled in a pre–HAART trial of HIV–infected individuals with memory complaints and CD4 counts less than 300 found a prevalence rate of 20% for asymptomatic neuropathy and 35% for symptomatic neuropathy. The estimated incidence rate of symptomatic distal sensory neuropathy was 36% after 12 months and 52% after 24 months (Schifitto et al 2002). In the age of HAART therapy, the same group found the 1–year incidence of symptomatic distal sensory neuropathy decreased to 21% (Schifitto et al 2005).
When approaching the diagnosis and management of these complications, it is essential to determine 4 things: (1) the specific localization of the lesion (ie, spinal cord, nerve root, plexus, peripheral nerve, or multiple peripheral nerves); (2) the staging of the HIV infection (determined by the total CD4+ lymphocyte cell count, the total HIV viral load, and the patient's clinical condition); (3) the patient's medication regimen; and (4) the presence of concomitant disease processes.

Localizing the lesion may be challenging because multiple points of the neuraxis may be simultaneously involved, resulting in potentially perplexing clinical presentations.

Clinical manifestations

The spectrum of clinical manifestations is wide given that the peripheral nerve can be affected at any point from the level of the root to the most distal small, unmyelinated fibers. The etiology of the findings is usually due to a direct effect of HIV itself, opportunistic infections, neoplasms, or medication toxicity. The clinical presentation and etiology of the reported HIV complications of the peripheral nervous system will be considered individually, moving from the root level distally to the peripheral nerve.

Polyradiculopathy. HIV-related lumbosacral polyradiculopathy is characterized by asymmetric leg weakness involving proximal and distal muscles, flaccid paraparesis, hypo- or areflexia, sacral and lower extremity sensory loss, and sphincter disturbances such as urinary retention. The symptoms develop over a period of 1 to 6 weeks. The finding of “saddle” anesthesia, urinary retention, and a sensory level should raise suspicion for polyradiculopathy, rather than another process such as chronic inflammatory demyelinating polyneuropathy. In herpes zoster radiculitis, pain typically precedes a rash, which develops in a dermatomal distribution in the face or trunk. Motor involvement and weakness can also occur in more severe cases (McArthur 1987).

Cytomegalovirus infection has been identified as a cause of polyradiculopathy. It occurs in approximately 2% of patients with a CD4 cell count of 50 cells/µL or less (de Gans et al 1990). The patient typically presents with radiating, low back pain, progressive areflexic paraparesis,
and distal sensory loss. Two thirds of patients complain of urinary difficulties including hesitancy or retention (Brew 2003). Weakness is typically more prominent than sensory loss (Miller et al 1990). Cerebrospinal fluid evaluation may reveal polymorphonuclear pleocytosis, hypoglycorrhachia, and a raised protein concentration. Polymerase chain reaction of the cytomegalovirus DNA is positive in approximately 90% of affected patients (Cinque et al 1997). MRI of the lumbosacral spine may reveal thickened, enhanced nerve roots in approximately one third of patients (Bazan et al 1991; Talpos et al 1991; Kim and Hollander 1993). The classical electrophysiologic profile includes denervation of lower extremity and paraspinal muscles, with normal nerve conduction velocities and sensory potentials (Beydoun 1991). However, a coexisting HIV neuropathy causing abnormal sensory potentials could cause confusion.

Anticytomegalovirus therapy with ganciclovir, foscarnet, or a combination of both drugs is imperative because of the rapid progression. In 1 study of patients with AIDS and acute lumbosacral polyradiculopathy, 15 of 23 patients had cytomegalovirus infection, and treatment with ganciclovir was followed by stabilization (So and Olney 1991). Oral acyclovir is usually effective in herpes zoster radiculitis (Sawyer 1988).

Radiculopathy has also been associated with syphilis (Lanska et al 1988), lymphoma (Leger et al 1992; Fuller et al 1993), vasculitis (Oberlin et al 1989), toxoplasmosis (Kayser et al 1990), tuberculosis (Botzel 1993), primary CNS lymphoma with lymphomatous meningitis (Klein et al 1990), and herpes zoster (De La Blanchardiere et al 2000). Also, some data suggest that HIV itself may lead to a lumbosacral radiculopathy (So and Olney 1991).

Plexopathy. Bilateral brachial neuritis has been described at the time of seroconversion, occurring within 1 to 2 weeks of the acute febrile illness, with pain, weakness, scapular winging, and muscle atrophy (Levy et al 1985; Calabrese et al 1987; Brew et al 1989).

Mononeuropathies. The most common cranial mononeuropathy is facial nerve palsy, with less frequent involvement of cranial nerves II, V, and VIII (Levy et al 1985; Newman and Lessell 1992; Grimaldi et al 1993). Bilateral facial nerve palsies have also been reported with HIV infection (Wechsler
and Ho 1989; Serrano et al, 2007), most commonly occurring at the time of seroconversion, but also with advanced disease (Belec et al 1988; Murr and Benecke 1991), possibly secondary to opportunistic infection or lymphoma (Sasaki et al 2002). Herpes zoster, neurosyphilis, and hepatitis C have been associated with facial nerve palsies and should be excluded.

Other mononeuropathies, such as neuropathy of the laryngeal recurrent nerve (Samll et al 1989; Loddenkemper et al 2004) and bilateral phrenic nerves (Piliero et al 2004) have been reported in HIV-infected patients. These neuropathies may occur as isolated events or may precede the development of multiple mononeuropathies, ie, mononeuropathy multiplex.

Mononeuritis multiplex. The clinical pattern of mononeuritis multiplex is that of the simultaneous or sequential involvement of individual major peripheral nerves in different limbs, resulting in the often abrupt onset of symptoms in variable distributions. This syndrome may develop early or late in the course of HIV infection (So 1992). Several underlying etiologies of this syndrome should be recognized and include vasculitis, cryoglobulinemia, lymphoma, or cytomegalovirus infection.

Mononeuritis multiplex as a manifestation of polyarteritis nodosa, a vasculitis of medium–sized vessels, may occur at any stage of HIV infection. Though vasculitis classically presents as a mononeuritis multiplex, many patients present with an overlapping symmetrical sensorimotor polyneuropathy, or even a distal sensorimotor polyneuropathy, due to the cumulative involvement (Brannagan 1997). The neuropathy symptoms may be accompanied by weight loss, myalgias, and leg tenderness (Lange et al 1988; Said et al 1988; Gherardi et al 1993). Systemic manifestations, though less frequent, include renal failure, skin rash, testicular pain, arthritis, or hypertension. The erythrocyte sedimentation rate is usually elevated, and patients may be positive for hepatitis B surface antigen (Lange et al 1988; Fuller et al 1993).

Mononeuritis multiplex may also occur in association with an unspecified vasculitis (Gherardi et al 1993), involving small vessels with neutrophilic inflammatory vascular disease. A milder form is associated with a pathological picture of perivasculitis in which there are
perivascular inflammatory cells but no vasonecrosis or fibrosis (Lipkin et al 1985), with the neuropathy following a more benign course.


Invasion of the nerves by lymphoma or Kaposi sarcoma can also result in the clinical picture of mononeuritis multiplex (Levy et al 1985; Gold et al 1988; Fuller et al 1993).

A subset of HIV-infected patients develops a hyperimmune response to HIV infection by developing an oligoclonal expansion of CD8+ lymphocytes. Diffuse infiltrative lymphocytosis syndrome may develop due to diffuse visceral lymphocytic infiltration, particularly of the salivary glands and lungs (Itescu et al 1990; 1992; 1993; Franco-Paredes et al 2002). A sensorimotor polyneuropathy may develop due to angiocentric infiltration by CD8 cells and vascular mural necrosis (Gherardi et al 1998). In a series of 12 patients with diffuse infiltrative lymphocytosis syndrome and peripheral neuropathy, all had a sicca syndrome and multivisceral involvement. Four had an asymmetrical and 8 a symmetrical neuropathy. Nerve biopsy showed marked angiocentric CD8 infiltrates without mural necrosis and with abundant HIV p24 protein in macrophages. Improvement with AZT was seen in 6 out of 6 patients, and steroids were beneficial in 4 out of 5 patients. Two patients developed a primary B cell lymphoma (Moulignier et al 1997).

In later stages of HIV infection when patients have less than 50 CD4 cells, cytomegalovirus may result in a rapidly progressive multifocal neuropathy. This may be confirmed by demonstration of cytomegalovirus in the CSF by polymerase chain reaction accompanied by an elevated protein level and predominantly polymorphonuclear pleocytosis. Characteristic nerve biopsy findings include multiple foci of endoneurial necrosis, inflammatory infiltrates of mononuclear and polymorphonuclear cells, and cytomegalovirus inclusions in endothelial cells of endoneurial capillaries with surrounding inflammation (Said et al 1991; Roulet et al 1994). Treatment includes antivirals, such as ganciclovir, foscarnet, and cidofovir, along with immune reconstitution with HAART (Robinson–Papp et al 2009).
Distal polyneuropathy. A predominantly sensory, distal symmetric polyneuropathy is the most common peripheral manifestation seen in HIV–1 infection and typically has been reported to occur in later stages of the disease. In the era of HAART therapy, patients are living longer, and comorbidities not dependent on immunologic or virologic status are increasingly being recognized as important in the pathogenesis of distal symmetric polyneuropathy (Morgello et al 2004; Nakamoto et al 2010). These comorbidities include vitamin B12 deficiency, substance abuse (Lopez et al 2004), medications, and diabetes (Fichtenbaum et al 1995; Manji 2000). Hepatitis C co-infection is reportedly not associated with an increased risk of developing sensory neuropathy (Cherry et al 2010).

Older age, lower CD4 nadir, current combination antiretroviral therapy use, and prior “d–drug” therapy are significant risk factors for developing HIV sensory neuropathy (Ellis et al 2010; Nakamoto et al 2010).

Patients present with paresthesias typically distal to the ankles. Deep tendon reflexes at the ankles are depressed or absent, and intrinsic foot muscle weakness may be seen in 37% of patients (Cornblath and McArthur 1988). Sensory loss and spontaneous pain are frequently reported (Ellis et al 2010). Physical examination shows decreased distal vibratory and temperature sensation with increased or decreased sensitivity to pinprick in the toes. Strength and proprioception are generally preserved (Robinson–Papp and Simpson 2009).

Electrophysiologic findings are largely axonal, although demyelinating features have been described to a lesser degree (Bailey et al 1988; So et al 1988). Needle electromyography abnormalities are not typical, but chronic reinnervation changes may be seen (Robinson–Papp and Simpson 2009). Pathologic features include axonal degeneration of long axons in distal regions in a “dying back” pattern, with reduction of both small and large myelinated fiber densities (Cornblath and McArthur 1988; Griffin et al 1998; Araujo et al 2000). Small fiber nerve damage may be assessed by skin biopsy with quantification of the epidermal nerve fiber density. A decreased epidermal nerve fiber density is associated with greater pain intensity and higher HIV plasma RNA levels (Polydefkis et al 2002).
Qualitative changes (such as focal swellings) may precede development of symptomatic distal symmetric polyneuropathy and decreased epidermal nerve fiber density (Herrmann et al 2004; Ebenezer et al 2007). Occasionally, HIV may be cultured from the CSF of affected individuals (Hollander and Levy 1987).

Antiretroviral toxic neuropathy has been a well-described complication of exposure to nucleoside analogues, particularly zalcitabine (ddC), but also didanosine (ddl) and stavudine (d4T) (Dubinsky et al 1989; Lambert et al 1990; Cherry et al 2003), which are collectively known as “d–drugs.” Symptoms typically occur in the first 6 weeks of treatment, and the risk of developing a toxic distal symmetric polyneuropathy from a d–drug is usually maximal in the first 3 months of therapy. Although symptoms may subside with termination of treatment, complete resolution is atypical (Nakamoto et al 2010). The toxic effect is dose–dependent and is estimated to occur in 15% to 38% of patients receiving these drugs (Blum et al 1996; Dalakas 2001; Sacktor et al 2009). Although less commonly used in the Western nations, the “d drugs” remain a valuable therapy in the developing world (Sacktor et al 2009). The combination of these drugs with hydroxyurea is associated with an increased risk of sensory neuropathy, suggesting a possible synergistic effect between the drugs (Moore et al 2000).

The clinical presentation often resembles distal sensory polyneuropathy, with predominantly axonal, sensory electrophysiologic findings. Antiretroviral toxic neuropathy may sometimes be distinguished from distal sensory polyneuropathy by its more painful character, abrupt onset with initiation, and eventual amelioration following cessation of the medication (Berger et al 1993; Blum et al 1996; Moore et al 2000). There may also be a “coasting phenomenon” in which the symptoms intensify 2 to 4 weeks following withdrawal of the drug.

Neurotoxicity is associated with mitochondrial dysfunction via the inhibition of gamma–DNA polymerase, leading to depletion of the nerve’s mitochondrial DNA (Dalakas et al 2001). Pathologic studies have revealed prominent mitochondrial disruption and abnormalities of the cristae (Chen et al 1991; Patterson et al 2000). Neuropathy and acquired lipodystrophy may be manifestations of these mitochondrial effects (Brinkman et al 1999).
The protease inhibitor indinavir was found to be toxic to HIV-infected dorsal root ganglion cultures (Pettersen et al 2006). However, analysis of 1159 HIV-infected individuals enrolled in a large, prospective, observational multicenter study revealed no statistically significant association when adjustments were made for well-known concomitant risk factors (eg, older age, more advanced disease, greater exposure to neurotoxic d-drugs) (Ellis et al 2008).

Other medications used in the treatment of AIDS-related complications may also lead to polyneuropathy. Vincristine, a vinca alkaloid used in the treatment of solid tumors, such as Kaposi sarcoma, lymphoma, and leukemia, binds with tubulin and is believed to cause a distal axonopathy by affecting axonal transport (Topp et al 2000). Isoniazid for the treatment of tuberculosis and dapsone for the treatment of pneumocystis carinii pneumonia or toxoplasmosis may also cause neuropathy. The antifungal and antibacterial agent metronidazole may produce sensory neuropathy (Gondim et al 2005). Other potentially neurotoxic medications include chloramphenicol, ethambutol, etoposide, pyridoxine, and thalidomide (Robinson–Papp and Simpson 2009).

Inflammatory demyelinating polyneuropathy. HIV is also associated with acute or chronic inflammatory demyelinating polyneuropathies. These are characterized by weakness, absent deep tendon reflexes, elevated CSF protein, and improvement either spontaneously or due to immunomodulation (Cornblath et al 1987; Riggs et al 1987).

Acute inflammatory demyelinating polyneuropathies or Guillain–Barré syndrome may have a bimodal pattern of occurrence, developing at the time of seroconversion and prior to the appearance of HIV antibodies (Hagberg et al 1986; Piette et al 1986; Vendrell et al 1987; Brannagan and Zhou 2003; Wagner and Bromberg 2007) or during the chronic phase of HIV infection (Bani–Sadr et al 2002). Acute inflammatory demyelinating polyneuropathy has also been reported to occur as a complication of immune reconstitution (Makela et al 2002; Teo et al 2007).

Electrodiagnostic findings consistent with a primary demyelinating neuropathy (such as severe conduction velocity slowing, prolonged distal latencies, and conduction block) are typical; however, other acute inflammatory demyelinating polyneuropathy variants, such as a motor axonal variant, have been reported (Wagner and Bromberg 2007). CSF
pleocytosis in a patient with Guillain–Barre syndrome raises the possibility of HIV infection; however, it is frequently not seen (Brannagan and Zhou 2003). Cytomegalovirus inclusions in Schwann cells have also been found (Eidelberg et al 1986; Dalakas and Pezeshkpour 1988).

First line therapy is plasmapheresis or intravenous immunoglobulin (IVIg) as it is in HIV-negative patients with AIDP (Robinson–Papp et al 2009).

There have been reports of patients presenting with a syndrome of rapidly progressive weakness, simulating Guillain–Barre syndrome, typically in the setting of lactic acidosis or symptomatic lactatemia. This is presumed to result from mitochondrial toxicity of nucleoside analogue therapy, particularly D4T, causing eventual disruption of the electron transport chain (Wooltorton 2002; Rosso et al 2003; Simpson et al 2004; Capers et al 2011). The electrodiagnostic features are primarily axonal, and most patients have not responded to intravenous immunoglobulin or plasmapheresis (Marcus et al 2002). The Miller Fisher variant (ophthalmoplegia, ataxia, and areflexia) of Guillain–Barre syndrome has also been described in a patient receiving D4T therapy (Shah et al 2003).

These patients may be at increased risk of developing CIDP (Brannagan and Zhou 2003). CIDP tends to develop during the early stages of HIV infection, although it may occur in the setting of AIDS (Miller et al 1988; Przedborski et al 1988; Brannagan and Zhou 2003). The CSF studies may reveal pleocytosis and the presence of viral antigens. Inflammatory infiltrates, sometimes seen in sural nerve biopsies, consist of CD8+ lymphocytes and macrophages, some of which harbor HIV antigens (Dalakas and Cupler 1996).

Autonomic neuropathy. Autonomic neuropathy becomes clinically relevant in advanced stages of HIV disease (Ruttimann et al 1991), generally occurring in conjunction with distal sensory polyneuropathy. Presenting symptoms typically include postural hypotension or gastroparesis (Brew 2003). An increased incidence of papillary abnormalities (Gluck et al 2000) and denervation in the jejunal mucosa (Batman et al 1991) has been reported. Increased abnormalities by cardiovascular tests, such as prolongation of the QT interval (Villa et al 1995), may place the patients at risk during invasive procedures (Craddock et al 1987; Villa et al 1992). The HIV-associated adipose
redistribution syndrome has also been attributed to the adverse effects of antiretroviral drugs on autonomic neurons in the CNS that project to visceral or subcutaneous white adipose tissue compartments (Fliers et al 2003).

Clinical vignette

A 40-year-old man with HIV infection for 4 years complained of symmetrical pain in the soles of both feet. The pain was hard, sharp, and achy and had progressed over the past 3 and a half months. The pain was worse at night, and he reported hypersensitivity to touch with bedsheets or shoes. His symptoms began 1 month after starting the medication didanosine. Didanosine was replaced with stavudine; however, the symptoms persisted. He denied weakness or hand symptoms. He denied a history of alcohol or intravenous drug use, though he formerly used crack cocaine.

On neurologic examination, his mental status and cranial nerve functions were normal. His motor strength was normal without atrophy or fasciculations. Deep tendon reflexes were absent at the ankles. He had decreased sensation to vibration and pinprick in the legs distally. His gait was steady.

His CD4 count was 483, and his viral load was less than 200. The following lab studies were normal: hepatitis B and C antibody levels, BUN, creatinine, random glucose, vitamin B12 level, RPR, TSH, serum protein electrophoresis, and antisulfatide antibodies.

Amitriptyline, 75 mg at night, provided mild relief. Gabapentin, 600 mg 3 times daily, provided no benefit.

Five and a half months after the onset of his symptoms, stavudine was discontinued, and his antiretroviral regimen was changed to abacavir, efavirenz, and lamivudine. After 1 month, his pain improved briefly before worsening. He increased his gabapentin to 1200 mg 3 times daily, without any noticeable benefit. He had no improvement with zonisamide,
600 mg daily. Lamotrigine was begun at 25 mg per day, and a rash and gastrointestinal upset occurred. He was referred to a pain specialist.

Etiology

The etiology of the various peripheral nerve disorders is usually due to opportunistic infections, neoplasms, medication toxicity, or possibly secondary to invasion and destruction by HIV itself. (See Clinical Manifestations section for further details.)

Pathogenesis and pathophysiology

The mechanisms behind peripheral nerve complications of HIV have not been fully elucidated. Resulting disease is probably a multifactorial process with current data implicating: (1) toxicity due to macrophages, cytokines, antibodies, viral proteins, mitochondrial dysfunction, or oxidative damage; (2) direct infection; (3) nutritional deficiencies.

Toxicity due to macrophages and cytokines. HIV viral transcripts and antigens have been detected in perivascular and endoneurial macrophages (Esiri et al 1993; Yoshioka et al 1994). Activated macrophages may result in the elevated production of destructive neural toxins (such as tumor necrosis factor, interleukin–1, and interleukin–6) and the depressed production of others (Griffin et al 1994; Shapshak et al 1995; Jones et al 2005). High numbers of macrophages expressing MHC class II markers, tumor necrosis factor alpha, interleukin–1, and interleukin–6 were noted in sural nerve specimens from patients with painful sensory neuropathy (Griffin et al 1994). These macrophages may play a critical role in causing demyelination, allowing activated lymphocytes and macrophages access across the blood–nerve barrier (Dalakas and Cupler 1996). In a recent study, the dorsal root ganglia of HIV–infected patients were exposed to supernatants from HIV–infected and activated macrophages, resulting in neuronal retraction in the dorsal root ganglion neurons and oxidative stress in the neuronal cell body (Hahn et al 2008).
Proinflammatory cytokines and other mediators of inflammation have been demonstrated in the dorsal root ganglia of patients with HIV infection (Yoshioka et al 1994; Nagano et al 1996). TNF–alpha can activate HIV viral production of latently infected neural cells (Tornatore et al 1991; Swingler et al 1992) and induce apoptosis in neuroectodermal cells (Selmay et al 1991). Arachidonic acid, another substance released by activated macrophages, can activate neuronal NMDA receptors, resulting in an influx of calcium ions and stimulation of nitric oxide synthase. Additionally, macrophage-derived factors such as prostaglandin E2 and leukotrienes may sensitize C polymodal nociceptors, and contribute to the neuropathic pain and hyperpathia commonly seen in HIV–neuropathy (Griffin et al 1998).

Toxicity due to viral proteins. The HIV–1 viral envelope protein gp120 has been discovered to exert a toxic effect on neurons through activation of the complement cascade (Dalakas and Pezeshkpour 1988; Apostolski et al 1994) or activation of macrophages to secrete neurotoxic factors (Lipton 1992; Giulian et al 1993). The latter process may be enhanced by the loss of certain CD4 cells, which normally counteract macrophage activation by elaborating interleukin–4 and interleukin–10 (Choa et al 1993; Wesselingh et al 1994; Tyor et al 1995). Gp120 has been shown to bind to CXCR4, a chemokine receptor found on neurons and Schwann cells (Keswani et al 2003b) and can directly induce apoptosis or cellular dysfunction (Hesselgesser et al 1998; Gabuzda and Wang 2000). Direct epineurial application of gp120 has been implicated in inducing neuropathic pain (Herzberg and Sagen 2001).

Tat, a viral protein released from HIV–infected cells, is known to activate HIV viral expression, modifying several cellular functions with resulting neurotoxicity (Magnuson et al 1995). Tat, through upregulation of inflammatory cytokines, may facilitate entry of the virus into the central nervous system and play a critical role in the progression of neurologic impairment in the course of HIV–associated dementia (Rappaport et al 1999; Pu et al 2003).

Toxicity due to antibodies. There is some evidence that patients with HIV may have antibodies to components of the peripheral nerve, such as IgM antisulfatide (Briani et al 1996; De Gasperi et al 1996; Lopate et al 2002). A higher incidence of IgG sulfatide antibodies was noted in HIV patients with distal sensory neuropathy versus HIV patients without distal sensory neuropathy (Lopate et al 2005). HIV–related autoimmunity has
been related to the structural homologies between HIV-1 and immune-regulatory molecules and also to components of myelin, both in the CNS (Pahwa et al 1985) and PNS (Silvestris et al 1995).

Mitochondrial dysfunction. Mitochondrial abnormalities in axons and Schwann cells have been described in sensory nerves of patients with zalcitabine (ddC)-induced neuropathy. This dysfunction is attributed to inhibition of gamma-DNA polymerase, the enzyme responsible for mtDNA replication (Dalakas et al 2001). Variations in the mitochondrial genome (Luzhansky et al 2001; Chen et al 2002; Canter et al 2008) and cytokine genotype (Cherry et al 2008) may influence susceptibility to nucleoside reverse transcriptase inhibitor toxicity.

Oxidative damage. Gp41 may be neurotoxic by a mechanism involving induction of iNOS that has been studied in HIV dementia (Adamson et al 1999). Similar mechanisms may play a role in HIV neuropathy.

Direct infection. HIV has been shown to infect ganglion neural cells in vitro (Kunsch and Wigdahl 1991) and in vivo. The blood–nerve barrier is relatively permeable at the site of the dorsal root ganglion, and HIV DNA and RNA sequences have been demonstrated in the dorsal root ganglion neurons and supporting cells of patients with a predominantly sensory peripheral neuropathy (Brannagan et al 1997). Patients without neuropathy at a similar stage of HIV infection did not have evidence of the HIV genome in neurons. HIV viral RNA has also been amplified from sural nerve biopsies (de la Monte et al 1988; Dalakas et al 1994), and HIV C2V3 envelope sequences have been amplified from peroneal nerve samples obtained from HIV/AIDS patients (Jones et al 2005). As described previously, low levels of HIV replication have also been detected in the perivascular or supporting cells in the dorsal root ganglion (Yoshioka et al 1994). These findings, though suggestive of a correlation, do not prove that direct HIV infection of neurons results in neuropathy (Dalakas and Cupler 1996; Brannagan et al 1997). Because of the low level of neurons affected and the inability of techniques, such as immunohistochemistry, to demonstrate production of viral proteins, most investigators have focused on mechanisms other than direct HIV neuronal infection as the cause of neuropathy or HIV dementia.

Coinfection with HTLV-2 has been shown to increase the risk of HIV neuropathy (Dooneief et al 1996; Zehender et al 2002).
Nutritional deficiencies. Nutritional deficiencies resulting from anorexia, diarrhea, or malabsorption should be considered. Vitamin B12 deficiency was reported in some studies (Harriman et al 1989; Kieburtz et al 1991) but not confirmed by others (Robertson et al 1993; Trimble et al 1993; Veilleux et al 1995). Impaired production of nerve growth factor due to the depletion of CD4+ T-cells has been proposed as a possible mechanism. Acetyl-carnitine deficiency has also been reported in small studies of HIV patients taking dideoxynucleotide drugs (Famularo et al 1997), and its supplementation was beneficial in a small open-label study (Hart et al 2004). (See the Management section for further details.) Plasma carnitine levels were not correlated with severity of neuropathy in larger studies (Simpson et al 2001).

Epidemiology

See the Historical note and nomenclature section of this clinical summary.

Prevention

As the incidence and severity of HIV-associated distal symmetric polyneuropathy have been shown to be positively correlated with the plasma HIV viral load (Childs et al 1999; Simpson et al 2002), aggressive control of the underlying disease with maintenance of the CD4 count above 500 cells/µL remains the key preventive measure against peripheral nerve dysfunction (Tyor et al 1995; Martin et al 2000). Administration of picomolar amounts of the hormone erythropoietin was demonstrated to prevent sensory axonal degeneration and in vitro dorsal root ganglion neuronal death by both gp120 and ddC (a neurotoxic dideoxynucleoside drug) (Keswani et al 2004). One study has also found that specific polymorphisms in the hemochromatosis gene may confer protection from the development of neuropathy with exposure to dideoxynucleoside drugs (Kallianpur et al 2006).

Differential diagnosis
Certain neurologic complications are known to occur at particular stages of HIV infection; therefore, an accurate determination of the patient's viral load and CD4 cell count can lead to a more focused diagnostic evaluation. Acute demyelinating polyneuropathy (Guillain–Barre syndrome) and mononeuropathies are more commonly associated with the early phase of HIV disease, when the CD4 cell count is greater than 500 cells/µL. At the other end of the spectrum, distal sensory polyneuropathy, HIV–related lumbosacral radiculopathy, cytomegalovirus polyradiculopathy, cytomegalovirus–induced mononeuritis multiplex, medication–related neuropathy (antiretroviral drugs), and autonomic neuropathy occur more commonly in patients with AIDS or CD4 cell counts less than 200 cells/µL. Other conditions such as CIDP, mononeuritis multiplex, peripheral neuropathy in diffuse infiltrative lymphocytosis syndrome, syphilitic polyradiculopathy, hepatitis C neuropathy, HTLV type I neuropathy, and motor neuron disease syndrome have been more frequently described in moderately advanced disease, when the CD4 count is 200 to 500 cells/µL.

Dideoxynucleoside analogue drugs—eg, zalcitabine (ddC), didanosine (ddI), and stavudine (d4T)—(Cherry et al 2006) have been associated with distal sensory polyneuropathy. Antiretroviral medications have been implicated in autonomic dysfunction. In addition, medications used to treat opportunistic infections and tumors, such as dapsone, isoniazid, metronidazole, and vincristine, may also cause neuropathy.

Diagnostic workup

A careful history and examination is essential to determine the disease stage and to localize the area of involvement. Electromyography or nerve conduction studies are useful in determining the distribution of nerve involvement and the degree of axonal or demyelinating damage. A lumbar puncture may detect elevated protein levels in AIDP or CIDP (Bailey et al 1988; Cornblath and McArthur 1988) and pleocytosis in cytomegalovirus polyradiculopathy or mononeuritis multiplex (Roulet et al 1994). CSF studies may reveal evidence of HIV itself (Hollander and Levy 1987), cytomegalovirus (by polymerase chain reaction) (Roulet et al 1994), or elevated lactate levels, which suggest lymphoma (Gold et al 1988). MRI of the lumbosacral spine is rarely useful; however, enhancement of the cauda equina in cytomegalovirus polyradiculopathy has been described (Bazan et al 1991; Talpos et al 1991).
Skin biopsy of the calf and thigh may reveal a reduced intraepidermal nerve fiber density in patients with polyneuropathy (Polydefkis et al 2002) and has been used to follow the response to potentially therapeutic agents such as nerve growth factor (McArthur et al 2000; Schifitto et al 2001). Epidermal nerve fiber density assessment may have a role as a predictor of the development of symptomatic HIV neuropathy (Herrmann et al 2004; 2006) and may correlate with the clinical and electrophysiologic severity of the neuropathy (Zhou et al 2007). One study has shown that HIV+ individuals (including those without neuropathy symptoms) have an impaired capacity to regenerate these small nerve fibers (Hahn et al 2007).

Sural nerve biopsy is typically performed if the diagnosis remains unknown or if vasculitis, cytomegalovirus or lymphoma is suspected. The array of pathologic findings includes axonal loss, segmental demyelination and perivascular mononuclear cell infiltrates with complement or immunoglobulin deposition. The inflammatory cells usually are macrophages or T-lymphocytes, predominantly of the CD8+ cytotoxic or suppressor cell type.

Prognosis and complications

The staging of the HIV infection (determined by the total CD4+ lymphocyte cell count, the total HIV viral load, and the patient's clinical condition) is a determinant factor in the particular peripheral nerve complication that will occur. The staging also will affect the prognosis. With the advent of HAART, the incidence of some complications (eg, HIV-related lumbosacral radiculopathy, cytomegalovirus polyradiculopathy, cytomegalovirus-induced mononeuritis multiplex, medication-related neuropathy [antiretroviral drugs], and autonomic neuropathy) has diminished, whereas there has been an increase in the incidence of peripheral neuropathy, both distal sensory polyneuropathy and antiretroviral toxic neuropathy.

Management
The primary management goal is control of the underlying process with HAART.

Nerve growth factor, an important neurotrophin that modulates the activity of small sensory nerve fibers, was investigated as a potential target for intervention in distal sensory polyneuropathy. Nerve growth factor was safe and well-tolerated and significantly improved pain symptoms; however, there was no improvement of neuropathy severity as assessed by neurologic examination, quantitative sensory testing, and epidermal nerve fiber density (Schifitto et al 2001).

The management of demyelinating neuropathies, including AIDP and CIDP, is the same as for non–HIV–1 infected patients. Both conditions respond to plasmapheresis (Cornblath and McArthur 1988; Kiprov et al 1988) or IVlg (Chimowitz et al 1989; Malamut et al 1992). There is 1 case report of a patient who developed acute inflammatory demyelinating polyneuropathies during the chronic phase of HIV infection, who had dramatic resolution of the neuropathy following HAART therapy alone (Bani–Sadr et al 2002). Mononeuropathies in HIV–infected patients, particularly recurrent laryngeal and bilateral phrenic neuropathies, have been reported to respond to high–dose IVlg (Loddenkemper et al 2004; Piliero et al 2004). Corticosteroids may be beneficial in patients with a painful distal sensory polyneuropathy due to vasculitis (Bradley and Verma 1996).

Treatment of neuropathic pain symptoms remains a challenge (Brannagan 2003), with many medications showing little or no superiority to placebo. Typical agents include anticonvulsants, antidepressants, topical agents, and opioids.

Anticonvulsants. Gabapentin has been reported to be helpful (Newshan 1998; Hahn et al 2004); however, a randomized clinical trial did not demonstrate superiority to placebo (Hahn et al 2004; Phillips et al 2010). Nonetheless, it is a desirable treatment given the decreased incidence of drug–to–drug interactions (Romanelli et al 2000). A typical starting dose is 100 mg 3 times daily, with subsequent escalation up to as much as 3600 mg/day as tolerated.
Pregabalin is a GABA analogue that acts on the alpha-2-delta ligand of voltage-activated calcium channels. It is an FDA-approved treatment for diabetic neuropathy, postherpetic neuralgia, fibromyalgia, and partial seizures. A recent placebo-controlled trial, however, showed that pregabalin was well tolerated but no better than placebo for treatment of the painful symptoms of HIV neuropathy (Simpson et al 2010).

Lamotrigine has been proven in placebo-controlled trials to be effective for HIV-associated painful sensory neuropathies (Simpson et al 2000; 2003). Patients not receiving drugs known to induce the metabolism of lamotrigine started at a dose of 25 mg every other day for the first 2 weeks, with a target maintenance dose of 600 mg/day (300 mg twice daily). Patients who were receiving drugs known to induce the metabolism of lamotrigine started at a dose of 25 mg daily, with a target maintenance dose of 400 mg/day (200 mg twice daily).

Anticonvulsants, such as phenytoin and carbamazepine, which are highly protein-bound or induce cytochrome P450, should be avoided as they might affect the efficacy of protease inhibitors (Romanelli 2000). Valproate should also be used cautiously as it has been shown in vitro to stimulate HIV (Moog et al 1996) and cytomegalovirus replication (Kuntz-Simon and Orbert 1995).

Antidepressants. Tricyclic antidepressants and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) are the 2 major classes used in the treatment of neuropathic pain. Controlled studies of amitriptyline, mexiletine, memantine, and acupuncture have been negative (Kemper et al 1998; Kieburtz et al 1998; Shlay et al 1998; Schifitto et al 2006). Duloxetine is an SNRI that is an FDA-approved treatment for diabetic neuropathy. A typical starting dose is 30 mg daily, with slow titration up to a maximum of 120 mg daily. It is also being studied for HIV-related neuropathy.

Topical treatments. Capsaicin, the active component of chili peppers, is known to bind to the excitatory vanilloid receptor (TRPV1), which is expressed on small-diameter afferent neurons specialized for the detection of noxious sensations. By activating these receptors, the capsaicin initially produces a burning sensation, and at higher concentrations, desensitizes these nociceptors. Low concentrations are not effective in painful HIV neuropathy; however, a single application of a
high-concentration (8%) dermal patch (NGX-4010) was found to provide some benefit in a double-blind, randomized controlled trial involving 307 patients (Simpson et al 2008). This treatment is currently approved by the United States FDA for postherpetic neuralgia only. Topical lidocaine, in gel or patch form, has not been found to be effective (Estanislao et al 2004).

Others treatments. Oral acetyl-L-carnitine (1500 mg twice daily) has been demonstrated to result in a reduction in neuropathic pain and a significant increase in cutaneous innervation in 1 open cohort of 21 HIV-positive patients followed for up to 33 months (Hart et al 2004). In another study, pain improvement was noted with 3000 mg of acetyl-L-carnitine daily; however, no change in epidermal fiber density was noted after 24 weeks of therapy (Valcour et al 2009). In a double-blind, placebo-controlled trial involving patients with ATN, acetyl-L-carnitine (500 mg twice a day intramuscularly for 14 days, followed by 1000 mg twice a day orally for 42 days) was found to result in improved pain ratings versus placebo (Youle et al 2007).

Smoked cannabis in a monitored setting was shown to have efficacy in relieving pain in a controlled trial (Abrams et al 2007). In a randomized, crossover trial, 46% of patients experienced at least 30% pain relief, compared to 18% for placebo (Ellis et al 2009). In this study, cannabis of potency between 1% and 8% tetrahydrocannabinol was smoked 4 times daily for 5 consecutive days during each of 2 treatment weeks, separated by a 2-week washout period.

Randomized controlled trials of subcutaneous recombinant human nerve growth factor (rhNGF) showed that it was superior to placebo for pain relief (McArthur et al 2000; Phillips et al 2010). Studies of newer agents, such as subcutaneous prosaptide and intranasal peptide T, were negative (Phillips et al 2010).

Opioids have not been formally studied in painful HIV-related sensory neuropathy (Phillips et al 2010); however, they may be useful for moderate to severe neuropathic pain. Careful patient selection and screening for substance abuse is imperative.
Hypnosis has shown efficacy in clinical trials but due to limited access is not typically used in the clinical setting. Acupuncture has not been shown to be effective (Robinson–Papp and Simpson 2009).

Management of autonomic symptoms focuses on removing exacerbating factors, such as drugs, which might cause orthostatic hypotension or anticholinergic side effects. If salt supplementation and compressive stockings are ineffective for treating orthostatic hypotension, fludrocortisone may be tried. Promotility drugs such as cisapride may be used to treat gastroparesis. Sildenafil can help those with erectile dysfunction (Brew 2003).

The immunophilin ligand, FK506, was found to have a neuroprotective effect in an in vitro model of toxic neuropathy due to ddC. Some studies have indicated that neuroprotection is via inhibition of calcineurin, a calcium–dependent protein phosphatase (Keswani et al 2003a). The hematopoietic growth factor, erythropoietin, has also been shown to prevent sensory axonal degeneration and in vitro dorsal root ganglion neuronal death by both the HIV envelope protein gp120 and zalcitabine (ddC) (Keswani et al 2004).