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HIV-Associated Peripheral Neuropathy

Epidemiology, Pathophysiology and Treatment

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Contents

Abstract

Peripheral neuropathy is the most frequent neurological complication associated with human immunodeficiency virus type 1 (HIV) infection and advanced acquired immunodeficiency syndrome (AIDS). There are at least 6 patterns of HIV-associated peripheral neuropathy, although these diagnoses are often overlooked or misdiagnosed.

Distal symmetrical polyneuropathy (DSP) is the most common form of peripheral neuropathy in HIV infection. DSP occurs mainly in patients with advanced immunosuppression and may also be secondary to the neurotoxicity of several antiretroviral agents. Treatment of painful DSP is primarily symptomatic, while pathogenesis-based therapies are under investigation. Reduction or discontinuation of neurotoxic agents should be considered if possible.

Inflammatory demyelinating polyneuropathy (IDP) can present in an acute or chronic form. The acute form may occur at the time of primary HIV infection or seroconversion. Cerebrospinal fluid lymphocytic pleocytosis (10 to 50 cells/mm^3) is helpful in the diagnosis of HIV-associated IDP. Treatment consists of immunomodulatory therapy.

Progressive polyradiculopathy (PP) most commonly occurs in advanced immunosuppression and usually is caused by cytomegalovirus (CMV) infection. Rapidly progressive flaccid paraparesis, radiating pain and paresthesias, areflexia and sphincter dysfunction are the cardinal clinical features. Rapid diagnosis and treatment with anti-CMV therapy are necessary to prevent irreversible neurological deficits resulting from nerve root necrosis.

Mononeuropathy multiplex (MM) that occurs in early HIV infection is characterised by self-limited sensory and motor deficits in the distribution of individual peripheral nerves. In advanced HIV infection, multiple nerves in two or more extremities or cranial nerves are affected. Treatment includes immunomodulation or anti-CMV therapy.

Autonomic neuropathy may be caused by central or peripheral nervous system abnormalities. Treatment is supportive with correction of metabolic or toxic causes.

Diffuse infiltrative lymphocytosis syndrome (DILS) presents as a Sjögren's-like disorder with CD8 T cell infiltration of multiple organs. Antiretroviral therapy and steroids may be effective treatments.

A variety of peripheral neuropathies occur in patients with human immunodeficiency virus type 1 (HIV) infection.[1] These peripheral neuropathies are often overlooked or incorrectly diagnosed in patients with HIV.[2] The presence of peripheral neuropathy may be masked by coexisting central nervous system (CNS) dysfunction such as dementia, focal brain lesions or myelopathy. In patients with advanced acquired immunodeficiency syndrome (AIDS), the presence of peripheral neuropathy may be overshadowed by other systemic conditions.

Different forms of peripheral neuropathy occur with increased frequency at particular stages of HIV disease.[3] In patients with relatively preserved immune function, inflammatory demyelinating polyneuropathy (IDP) may be the first manifestation of HIV infection. As immunocompetence becomes significantly compromised (CD4 lymphocyte count below 50 cells/mm^3), other types of peripheral nerve involvement may occur secondary to the presence of opportunistic infections. For example, progressive polyradiculopathy (PP) or mononeuropathy multiplex (MM) may be secondary to cytomegalovirus (CMV) co-infection. It is critical to distinguish the different forms of peripheral neuropathies since pathogenic mechanisms and treatment approaches differ. This article reviews current knowledge concerning HIV-associated peripheral neuropathies, including epidemiology, pathogenetic mechanisms, clinical manifestations, treatment strategies and results of clinical trials (section 3).

1. Epidemiology

Peripheral neuropathy is the most frequent neurological complication of HIV infection.[4-6] There is a significant correlation between other neurological complications of HIV infection and the presence of peripheral neuropathy.[6] A prospective study found clinical and electrophysiological signs of distal symmetrical polyneuropathy (DSP) in 14 of 40 (35%) patients with AIDS.[7] Barohn et al.[8] reported a low incidence of peripheral neuropathy in 798 men infected with HIV, but the incidence increased to 17% in patients with AIDS. There is a very low rate of peripheral neuropathy in the paediatric population infected with HIV.[9,10] Peripheral neuropathy may be the presenting and only manifestation of HIV infection.[11] Subclinical autonomic nervous system involvement has been reported in a significant number of patients infected with HIV who otherwise do not have neurological symptoms.[12] Both central and peripheral nervous system abnormalities may cause autonomic impairment.[13] Persistent CD8 hyperlymphocytosis in patients infected with HIV may occur in a variety

of clinical disorders including DSP, toxic DSP, MM, and IDP.[14]

2. Pathophysiology

In an autopsy study of 25 patients with AIDS, sural nerve pathology in 12 of 25 (48%) specimens showed loss of myelinated fibres with disproportionately greater loss of large myelinated fibres.[15] In a study of 21 patients with symptoms of DSP, there was evidence of demyelination and axonal degeneration in 19 of 20 (95%) sural nerve specimens.[16] In patients with DSP, mild epineural and endoneural perivascular inflammatory cells, such as T lymphocytes and activated macrophages, were observed in up to two-thirds of nerve specimens.[17] Mild mononuclear infiltration with some loss of dorsal root ganglion cells has been observed in association with selective gracile tract degeneration in upper thoracic and cervical segments in 4 of 27 patients with DSP.[18] In severely immunocompromised patients with IDP, nerve biopsy specimens showed only axonal degeneration with mild inflammatory changes.[18]

The lack of CD4 receptor expression in the nerve surface suggests that direct infection with HIV is unlikely.[19] Nerve biopsy specimens from patients with IDP may show isolated or mixed macrophage-mediated segmental demyelination and axonal degeneration.[20] Gherardi et al.[21] reported replication of HIV in nerve specimens from patients with AIDS with vasculitis. Autopsy studies of patients with PP have revealed nuclear and cytoplasmatic cytomegalic inclusions within endothelial, ependymal and Schwann cells consistent with primary CMV infection.[22]

In patients with HIV-associated MM and CD4 lymphocyte counts above 200 cells/mm^3, nerve biopsy specimens have shown axonal degeneration with perivascular inflammatory infiltrates in the majority of cases. However, in advanced immunosuppression, nerve biopsy specimens from AIDS-associated MM have shown mixed demyelination and axonal degeneration, accompanied by polymorphonuclear infiltrates characteristic of CMV. Electron microscopic studies in these nerve biopsy specimens have revealed CMV virions in mononuclear and endothelial cells.[23]

Pathological studies in patients with HIV-associated autonomic nervous system involvement have demonstrated abnormalities of the autonomic nerves at the jejunal mucosa, paraventricular nucleus and cervical sympathetic ganglia.[24,25] Patients infected with HIV may develop persistent CD8 hyperlymphocytosis with secondary peripheral nerve angiocentric immunoproliferative lesions as a part of the HIV-associated diffuse infiltrative lymphocytosis syndrome.[14]

3. Clinical Manifestations and Diagnosis

HIV-associated peripheral neuropathy may present with a variety of clinical manifestations at different particular stages of HIV infection. The most common forms of peripheral neuropathy observed in patients infected with HIV are highlighted in table I.

3.1 Distal Symmetrical Polyneuropathy

The major clinical symptoms of DSP are distal numbness, paresthesias and dysesthesias ('burning feet'), usually occurring symmetrically in the lower extremities. Distal and symmetrical numbness of the upper extremities may occur later in the course of DSP. The most common signs of DSP on neurological examination are absent or depressed ankle reflexes.[26,27] While joint position remains relatively normal, vibratory thresholds are increased in the feet. Pain and temperature sensation is reduced in a stocking and glove distribution. Motor examination generally reveals minimal weakness, usually restricted to intrinsic foot muscles.

The antiretroviral agents didanosine (ddI), zalcitabine (ddC) and stavudine (d4T) have well recognised dose-limiting neurotoxicity.[28,29] The reported incidence of neurotoxic neuropathy varies among different clinical trials. Early phase I studies of stavudine revealed a high incidence of toxic neuropathy in patients receiving high doses. We performed an analysis of peripheral neuropathy in a large primary antiretroviral trial,[2] evaluating zidovudine (AZT), didanosine and zalcitabine in

Table I. Summary of HIV-associated peripheral neuropathies, clinical manifestations and diagnosis (reproduced from Wulff and Simpson,[26] with permission)

Diagnosis	HIV disease stage	Clinical symptoms	Neurological signs	Diagnostic studies
Distal symmetric polyneuropathy	Late	Distal symmetric numbness, tingling and burning sensations; parasthesias or aching	Stocking-glove sensory loss; depressed or absent ankle reflexes	EMG: distal axonopathy
Inflammatory demyelinating polyneuropathy	Early>>late	Progressive weakness; paresthesias	Muscle weakness; mild sensory loss; areflexia	CSF: lymphocytic pleocytosis (10 to 50 cells/μL); EMG: demyelination
Mononeuritis multiplex	Early (limited) Late (progressive)	Foot or wrist drop; facial weakness; focal pain	Multifocal cranial and peripheral neuropathies	EMG: multifocal axonal neuropathies
Progressive polyradiculopathy	Late	Lower extremity weakness; sphincter dysfunction; paresthesias	Flaccid paraparesis; saddle distribution anesthesia; depressed ankle and knee reflexes	CSF: increased PMNs; EMG: polyradiculopathy
Autonomic neuropathy	Late>>early	Orthostatic dizziness; syncope; diarrhoea; anhidrosis; palpitations; impotence; urinary dysfunction	Orthostatic hypotension; pupillary abnormalities; sweating dysfunction; resting tachycardia	ECG: arrhythmias; blood pressure: orthostatic hypotension

CSF = cerebrospinal fluid; **ECG** = electrocardiography; **EMG** = electromyography; **PMNs** = polymorphonuclear leukocytes.

monotherapy and combination therapy arms. Entry criteria included CD4 count of between 200 and 500, thus, a high baseline incidence of HIV neuropathy would not be expected. The only group in this study with a significantly increased incidence of DSP was the zidovudine/zalcitabine arm (6%).

The pathogenesis of these toxic neuropathies is thought to be due to their interference with mitochondrial DNA synthesis. Decreased levels of acetyl-carnitine have been reported in patients with neurotoxic DSP.[30] Nutritional deficiencies, such as cyanocobalamin (Vitamin B12), infectious agents, such as CMV, and certain agents used in the management of AIDS-related complications, including vincristine,[31] isoniazid[32] and thalidomide[33] may also cause DSP. The susceptibility for developing toxic DSP is greater in those patients with advanced immunosuppression and when there is a history of neuropathy, irregardless of cause. Clinical examination does not reliably distinguish between HIV-associated DSP and neurotoxic DSP.

The diagnostic approach to patients with HIV infection and DSP consists of a comprehensive neurological history and examination, and appropriate blood studies in order to exclude other potential causes of neuropathy including diabetes mellitus, vitamin deficiencies, hereditary factors, alcoholism and other associated infectious agents, such as CMV or Lyme disease. In complex situations, electrodiagnostic studies, cerebrospinal fluid (CSF) analysis and sural nerve biopsy may be helpful.

3.2 Inflammatory Demyelinating Polyneuropathy

The prevalence of IDP in the HIV-infected population is unknown but it appears to be a relatively infrequent complication. There are two clinical forms of HIV-associated IDP. The acute form may occur at the time of the primary HIV infection or seroconversion.[34] Acute IDP is clinically characterised by rapidly progressive ascending weakness associated with generalised areflexia. The chronic form is distinguished by its slower progression and may be monophasic or relapsing. The pathogenesis of IDP is thought to be autoimmune.[35] In nerve biopsy specimens from late-stage patients with chronic form IDP (CIDP), CMV inclusions in Schwann cells have been found.[36]

CSF lymphocytic pleocytosis (10 to 50 cell/mm^3) provides useful information in distinguishing pa-

tients with HIV infection with IDP from those without HIV infection. However, since CSF pleocytosis is not present in all seropositive patients with IDP,[20] HIV infection must still be considered in all patients with IDP. CSF protein is usually elevated (50 to 200mg/dL) in seropositive as in seronegative patients with CIDP.[20]

3.3 Progressive Polyradiculopathy

PP is most common in advanced immunosuppression, when CD4 lymphocyte counts are below 50 cells/mm^3 and other AIDS-defining opportunistic infections are present. Many patients have coexistent systemic CMV infection such as retinitis.[37] The most common aetiological agent of PP in patients with AIDS is CMV, followed less commonly by neurosyphilis and lymphomatous meningitis.[22]

The most common clinical presentation of PP is a rapidly progressive flaccid paraparesis. Other manifestations of PP include radiating pain and paresthesias in the cauda equina distribution, lower extremity areflexia, mild sensory loss and sphincter dysfunction. A thoracic sensory level may be found in some patients,[22] and upper extremities may be involved late in the course of PP.[23]

CSF findings in CMV-related PP are characterised by a marked polymorphonuclear pleocytosis, elevated protein level (above 50mg) and hypoglycorrhachia.[37] Lymphomatous meningitis is characterised by a lymphocytic pleocytosis. Radiological studies of the spinal cord should be performed to exclude focal compressive lesions of the cauda equina. In patients with PP, the diagnostic assay of choice is polymerase chain reaction (PCR) of CSF for CMV.[38]

3.4 Mononeuropathy Multiplex

MM is an infrequent complication in HIV infection. MM is characterised by multifocal sensory or motor abnormalities involving individual peripheral cutaneous and mixed nerves, nerve roots or cranial nerves.[39] Electrophysiological and pathological features of MM may overlap with DSP and IDP. Early in the course of HIV infection, when CD4 lymphocyte counts are greater than 200 cells/mm^3, MM is characterised by the acute onset of sensory deficits limited to 1 or 2 peripheral or cranial nerves. In patients with early HIV infection, MM is thought to be mediated by immune mechanisms and is usually self-limited.[1] As HIV disease advances and immunosuppression progresses, a more extensive and rapidly progressive form of MM may occur. This late form of MM involves multiple nerves in two or more extremities or multiple cranial nerves,[40] and often results from direct CMV infection of peripheral nerves.[23] CSF analysis reveals nonspecific abnormalities, such as elevated protein and mild mononuclear pleocytosis. PCR for CMV DNA and nerve biopsy may provide more specific diagnostic data.[40]

3.5 Autonomic Neuropathy

The prevalence of autonomic dysfunction in HIV-infected patients is not known. Case series have reported subclinical autonomic nervous system involvement in otherwise neurologically asymptomatic patients infected with HIV, whereas patients with AIDS have more frequent and severe autonomic involvement.[12,41] Failure of the parasympathetic autonomic system is manifested clinically by resting tachycardia, impotence and urinary dysfunction. Sympathetic system abnormalities include orthostatic hypotension, syncope, diarrhoea and anhidrosis. A variety of factors may contribute to autonomic dysfunction, including central and peripheral nervous system abnormalities, dehydration, malnutrition and medications such as vincristine, tricyclic antidepressants and pentamidine.

3.6 Diffuse Infiltrative Lymphocytosis Syndrome

DILS resembles Sjögren's syndrome, and is associated with multivisceral CD8 T-cell infiltration, involving salivary glands, lungs, kidneys, gut and peripheral nerves.[14,42] DILS occurs in a subset of patients infected with HIV who develop persistent CD8 hyperlymphocytosis. DILS-associated neuropathy has a variety of clinical presentations including painful symmetric or asymmetric sensorimotor neuropathy, distal sensory neuropathy, mononeur-

itis multiplex and demyelinating polyneuropathy.[14] Host inflammatory responses to HIV infection may be responsible for peripheral nerve involvement in DILS.

4. Treatment

An algorithm for diagnosis and management of peripheral neuropathy associated with HIV infection is shown in figure 1 and table I. Treatment options are summarised in table II.

4.1 Distal Symmetrical Polyneuropathy

The first step in the treatment of DSP, after metabolic causes are excluded, is the consideration of withdrawal or dose reduction of neurotoxic antiretroviral agents (didanosine, zalcitabine and stavudine). In neurotoxic DSP, the standard time for resolution of neuropathy, after discontinuation of a neurotoxic antiretroviral agent, is approximately 4 to 8 weeks. In certain patients, resolution may take up to 16 weeks.[29] Some patients may experience a 'coasting period' of 4 to 8 weeks following withdrawal of the drug, during which time the symptoms of neuropathy may intensify before improving. When the neurotoxic agent plays an important role in the maintenance of virological control and particularly when there are limited alternative antiretroviral drugs available to the patient because of drug resistance or intolerance, it may be appropriate to continue the antiretroviral drug.

The current treatment of DSP is primarily symptomatic. There is considerable variability in the therapeutic strategies in painful DSP. The guidelines of the World Health Organization 'analgesic ladder'[43] serve as a helpful approach to painful DSP. The guidelines suggest starting with non-opioid analgesics, such as paracetamol (acetaminophen) and nonsteroidal anti-inflammatory agents in patients with mild pain. Adjuvant agents such as antidepressants or anticonvulsants may provide added benefit. Increasing levels of pain call for a mild opioid combination (e.g. paracetamol and codeine) with an adjuvant. For severe pain, a strong opioid or long-lasting opioid agonist (e.g. methadone, long-acting morphine or fentanyl) may be considered.

Although a controlled study of amitriptyline and mexiletine showed that neither was superior to placebo in the treatment of painful HIV neuropathy,[44] low dose tricyclic antidepressants (10 to 25 mg/day) may be helpful in some patients. Other patients may require antidepressant dosage levels (100 to 150 mg/day) for effect, although there may be dose-limiting toxicities such as sedation.

Most anticonvulsants such as gabapentin, phenytoin and carbamazepine have not been investigated in placebo-controlled clinical trials but may provide relief of pain in some patients with HIV-associated painful DSP. The use of carbamazepine may be limited by the development of leukopaenia, particularly in patients with HIV, where leukopaenia and anaemia are often already present. In a small placebo-controlled study, lamotrigine was effective in reducing pain in AIDS–associated DSP.[45] Rash was the most common adverse effect. In order to minimise the occurrence of allergic rash, lamotrigine should be initiated at a low dosage (e.g. 25 mg/day or every other day) and this increased over approximately 6 to 8 weeks to 300 to 400 mg/day. A larger placebo-controlled study of lamotrigine in HIV is underway.

Topical capsaicin has been generally unsuccessful in small studies of painful HIV neuropathy.[1] In an open label trial, a 5% topical lidocaine gel was effective in reducing pain in AIDS–associated DSP.[46] A placebo-controlled trial of this gel in the treatment of painful AIDS neuropathy is under analysis. While alternative therapies are widely used in HIV, most have not been assessed in clinical trials. Acupuncture was not superior to a control acupuncture arm using sham non-meridian points in the relief of painful HIV neuropathy.[47]

Pathogenesis-based therapies such as recombinant human nerve growth factor (rhNGF) have been investigated. NGF acts as a trophic factor in the developing and damaged peripheral nervous system.[48] In a phase II clinical trial in 270 patients with painful HIV neuropathy, subcutaneous rhNGF was superior to placebo in reducing pain after 18 weeks of blinded treatment.[49] The results of a 70 week open label extension period are under analysis.

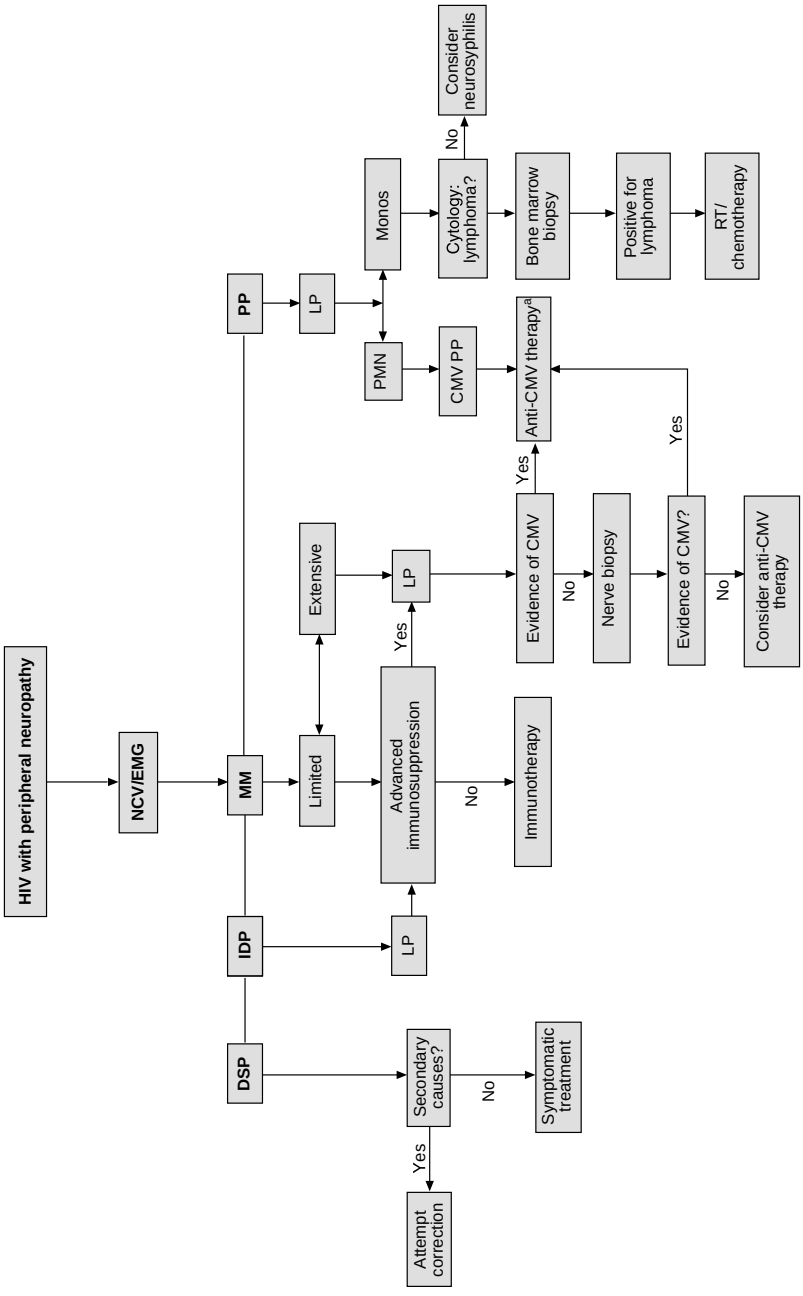

Fig. 1. Algorithm for management of peripheral neuropathy associated with HIV infection (reproduced from Wulff and Simpson,[26] with permission).
a Ganciclovir, foscarnet, cidofovir (singly or in combination).
CMV = cytomegalovirus; **DSP** = distal symmetrical polyneuropathy; **EMG** = electromyography; **IDP** = inflammatory demyelinating polyneuropathy; **MM** = mononeuropathy multiplex; **LP** = lumbar puncture; **Monos** = mononuclear cells; **NCV** = nerve conduction velocity; **PMN** = polymorphonuclear leucocytes; **PP** = progressive polyradiculopathy; **RT** = radiotherapy.

Table II. Summary of HIV-associated peripheral neuropathies and treatment (reproduced from Wulff and Simpson,[26] with permission)

Diagnosis	Therapy
Distal symmetric polyneuropathy	Neurotoxin withdrawal; analgesics; topical agents (5% lidocaine gel); anticonvulsants; tricyclic antidepressants; clinical trials
Inflammatory demyelinating polyneuropathy	Immunotherapy[a]; anti-CMV therapy[b] (late-stage HIV disease)
Mononeuritis multiplex	Early: immunotherapy[a] Late: anti-CMV therapy[b]
Progressive polyradiculopathy	Anti-CMV therapy[b]
Autonomic neuropathy	Neurotoxin withdrawal; elastic stockings, fluid and electrolyte replacement; fluorocortisone, antiarrhythmic agents

a Corticosteroids, plasmapheresis, high-dose intravenous immunoglobulin.

b Ganciclovir, foscarnet, cidofovir (singly or in combination).

CMV = cytomegalovirus.

While phase II studies of rhNGF in HIV sensory neuropathy yielded positive results,[50] 2 large phase III studies of diabetic neuropathy did not show significant efficacy.[49] Future clinical development of rhNGF for diabetic and HIV neuropathy is uncertain. Other pathogenesis-based therapies under consideration for the treatment of HIV neuropathy include prouridine, levocecarnine (acetyl l-carnitine) and neurophilins.

4.2 Inflammatory Demyelinating Polyneuropathy

Although controlled studies have not been reported, case series have shown that IDP may respond to immunomodulating therapy, such as plasmapheresis (4 to 5 exchanges) or high-dose intravenous immunoglobulin (0.5 to 1.0 gm/kg over 2 days).[20] In patients with severe immunosuppression (e.g. CD4 lymphocyte counts below 50 cells/mm^3), particularly when CSF PCR or nerve biopsy reveals evidence of CMV infection,[36,40] antiviral therapy with ganciclovir (5 mg/kg intravenously twice daily), foscarnet (90 mg/kg every 12 hours), or cidofovir (5 mg/kg every 2 weeks), singly or in combination, is recommended.[51]

4.3 Progressive Polyradiculopathy

The rapidly progressive course and good response to early therapy of PP demand prompt diagnosis and treatment in order to prevent irreversible neurological deficits due to nerve root necrosis. Several case series indicate that PP may respond to anti-CMV therapy, as in IDP, as discussed in section 4.2.[37] Newer drugs for the management of CMV infection include valganciclovir, cidofovir and fomivirsen (an antisense oligonucleotide).[51] A prospective trial of antiviral agents in the treatment of HIV-associated CMV neurological disease was suspended because of limited accrual resulting from the reduced incidence of CMV disease in the current era of highly active antiretroviral therapy (HAART) [unpublished data].

4.4 Mononeuropathy Mulitplex

The peripheral nerve lesions of the early form of HIV-associated MM usually remit spontaneously within several months.[52] In patients with incomplete recovery, immunomodulating therapy, including corticosteroids (60 to 80 mg/day), plasmapheresis, or high-dose intravenous immunoglobulin may provide benefit.[17] Patients with late stage AIDS (CD4 count less 50 cells/mm^3) should be treated with anti-CMV therapy,[40] even in the absence of conclusive evidence of CMV infection.

4.5 Autonomic Neuropathy

Drugs potentially causing autonomic neuropathy, including tricyclic antidepressants, should be discontinued if possible. Volume depletion should be corrected. Supportive management includes use of waist-high stockings or abdominal binders, increased intake of caffeine, liberal fluid and salt intake, and eating frequent small meals. Manoeuvres such as squatting and standing with crossed legs, along with reconditioning exercises can be helpful. Use of agents such as oral fludrocortisone (0.05mg twice daily initially and up to 0.1 to 0.3mg twice daily), oral midodrine (5mg morning and evening) and antiarrhythmic agents are potential treatments

for HIV-associated autonomic dysfunction.[53,54] Care must be taken to avoid supine-hypertension.

4.6 Diffuse Infiltrative Lymphocytosis Syndrome

Zidovudine and immunomodulating agents, such as corticosteroids have been reported to be effective in some patients with DILS.[42]

5. Conclusion

While peripheral neuropathies are the most common neurological complications in patients with HIV and AIDS, their diagnosis and treatment are often delayed. While these are generally not life-threatening disorders, they produce significant morbidity. Clinicians caring for such patients must be familiar with the clinical manifestations of peripheral neuropathies in order to provide prompt diagnosis and treatment. Appropriate therapy may result in marked improvement in quality of life. In the current era of HAART and the consequent prolongation of patients' lives, it is likely that the frequency of HIV-associated neurological complications will increase. Advances in basic and clinical research should improve our understanding of these disorders, and lead to improvements in their diagnosis and treatment.

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