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Selected peripheral neuropathies associated with human immunodeficiency virus infection and antiretroviral therapy

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A variety of peripheral neuropathies are associated with human immunodeficiency virus (HIV) infection. Although the incidence of certain forms of neuropathy is increased in HIV infection, in other cases, the association may be fortuitous. Different forms of peripheral neuropathy occur with increased frequency at particular stages of HIV disease. For example, inflammatory demyelinating neuropathy (IDP) is often the first manifestation of HIV disease, when CD4 lymphocyte counts are relatively high. As immunosuppression progresses and HIV viral load becomes uncontrolled, the incidence of distal symmetrical polyneuropathy (DSP) increases. In advanced stages of HIV disease (CD4 count $<$50 cells/mm^3), patients may develop opportunistic cytomegalovirus (CMV) nerve infection, which can present as progressive polyradiculopathy (PP) or mononeuropathy multiplex (MM). In addition to the neuromuscular disorders caused by HIV and its concomitant immunosuppression, the use of antiretroviral (ARV) drugs and other therapeutic agents in HIV disease is frequently limited by neuromuscular side effects. This paper will review the symmetrical forms of polyneuropathy that occur in association with HIV infection and nucleoside analogue therapy. The clinical, electrophysiologic, and pathologic features of these disorders will be described along with a discussion of theories of pathogenesis and results of treatment to date. *Journal of NeuroVirology* (2002) **8(suppl. 2),** 33–41.

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Distal symmetrical polyneuropathy

Distal symmetric polyneuropathy (DSP) may be diagnosed in over 30% of patients with acquired immunodeficiency syndrome (AIDS), after other recognized causes for polyneuropathy are excluded (So *et al*, 1988). DSP is usually associated with late stages of human immunodeficiency virus (HIV) disease, as indicated by the presence of opportunistic infections and significant wasting in the majority of patients with DSP (Lange *et al*, 1988; Leger *et al*, 1989; So *et al*, 1988). Data from several clinical trials including the author's longitudinal cohort study indicate that the incidence of DSP is greater in the strata of patients with low CD4 counts as well as those with high HIV viral load (Barohn *et al*, 1993; Childs *et al*, 1999; Schiffito *et al*, 2002; Simpson *et al*, 1994). In a study of subjects with advanced immunosuppression, 55% had evidence for DSP at baseline assessment (Schiffito *et al*, 2002).

Clinical features

The major symptoms of DSP are distal dysesthesias, almost always beginning in the lower extremities (Table 1). A complaint of "burning feet" is reported by 23% to 100% of AIDS patients evaluated for DSP

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Table 1 Major neuromuscular syndromes in HIV disease

Diagnosis	*Disease stage*	*Presenting symptoms*	*Neurological signs*	*Diagnostic studies*	*Therapy*
DSP	Late	Distal numbness Paresthesias Burning pain	Stocking-glove sensory loss Ø ankle reflexes	EMG: distal axonopathy	Neurotoxin withdrawal Analgesics Tricyclic antidepressants Anticonvulsants Capsaicin
IDP	Early ≫ late	Progressive weakness Paresthesias	Weakness Areflexia Mild sensory loss	CSF: mild ↑ WBC; ↑↑ protein EMG: demyelination	Early: plasmapheresis steroids, IVIg Late: ganciclovir, foscaret, cidofovir
MM	Early (limited) Late (progressive)	Facial weakness Foot or wrist drop Focal pain	Multifocal, cranial, and peripheral neuropathies	EMG: multifocal axonal neuropathy Nerve biopsy: inflammation, vasculitis, CMV inclusions	Early: none Late: ganciclovir, foscaret, cidofovir
PP	Late	Lower extremity weakness Paresthesias Urinary dysfunction	Flaccid paraparesis Saddle anesthesia Ankle and knee reflexes	CSF: WBC (PMNs) + CMV culture EMG: polyradiculopathy	Ganciclovir Foscarnet Cidofivir
Myopathy	All	Proximal muscle weakness Myalgias Wasting	Proximal muscle strength	CK EMG: ± irritative Muscle biopsy: myofiber degeneration, ± inflammation	ZDV-withdrawal Corticosteroids
ALS-type syndrome	Late	Weakness Dysphagia	Weakness, limb ± bulbar Atrophy, fasciculations Hyperreflexia	EMG: neurogenic Pathology: motor neuron loss	ZDV, other ARV

DSP: distal symmetrical polyneuropathy; IDP: inflammatory demyelinating polyneuropathy; MM: mononeuropathy multiplex; PP: progressive polyradiculopathy; EMG: electromyography; CSF: cerebrospinal fluid; WBC: white blood cells; PMNs: polymorphonuclear leukocytes; CMV: cytomegalovirus; CK: creatine kinase levels; IVIg: intravenous immunoglobulin; ZDV: zidovudine; ARV: antiretrovirals.

in different series (Cornblath and McArthur, 1988; Lange *et al*, 1988; So *et al*, 1988). These patients may alter their gait to avoid pressure on their soles and often report that even the lightest contact (i.e., socks, bed sheets) increases their pain (Cornblath and McArthur, 1988). Numbness and paresthesias are also frequent symptoms of DSP. The upper extremities may be affected in a distal and symmetrical fashion later in the course of DSP. Muscle weakness is not a prominent symptom of DSP, and generally occurs only late in disease (Cornblath and McArthur, 1988).

The most common signs of DSP in AIDS are depressed or absent reflexes at the ankles relative to the knees (Cornblath and McArthur, 1988; Lange *et al*, 1988; So *et al*, 1988). The presence of hyperactive knee reflexes and depressed ankle reflexes may indicate concurrent myelopathy and neuropathy, which is a common association in HIV-infected individuals (Dal Pan *et al*, 1994). Vibratory thresholds are increased, and pinprick and temperature are reduced in a stocking and glove distribution whereas joint position sensation is relatively normal (Leger *et al*, 1989). Weakness is generally restricted to intrinsic foot muscles (Cornblath and McArthur, 1988; So *et al*, 1988).

The diagnosis of DSP is usually straightforward, when made by a clinician familiar with neurological clinical diagnosis, and the neurological complications of HIV infection. However, data from the AIDS Clinical Trials Group (ACTG) Protocol 175 reveals that DSP is often misdiagnosed even by experienced clinical investigators in AIDS (Simpson *et al*, 1998). Marra and colleagues (1998) reported that a brief screening examination, performed by trained nonphysicians, correlates well with the diagnosis of DSP as made by an experienced neuro-AIDS neurologist. In that study of 199 subjects, after excluding patients with confounders for neuropathy, 42 (21%) had DSP. The diagnosis of DSP was associated with neurotoxic antiretroviral use and advanced HIV disease. Of 42 patients with DSP, 30 (71%) had no symptoms of neuropathy. In follow-up, most became symptomatic. In the cohort with advanced immunosuppression described above (Schiffito *et al*, 2002), 20% had asymptomatic DSP, whereas 35% were symptomatic. The use of neurotoxic dideoxynucleoside therapy was not associated with DSP.

Laboratory features

The electrodiagnostic features of DSP in AIDS are indicative of distal and symmetrical degeneration of sensory and motor axons, in a pattern similar to other forms of DSP. Small or absent sural nerve action potentials are the most common abnormalities in patients with DSP (Chavanet *et al*, 1989; Cornblath and McArthur, 1988; Fuller *et al*, 1991; Tagliati *et al*, 1999), although occasional patients with DSP and normal nerve conduction studies (NCSs) have been reported (Cornblath and McArthur, 1988; Lange *et al*, 1988; Leger *et al*, 1989; Snider *et al*, 1983).

DSP may be detected pathologically in nearly all patients dying with AIDS (Griffin *et al*, in press). The most common nerve biopsy finding in patients with DSP is degeneration of myelinated and unmyelinated axons (De la Monte *et al*, 1988; Griffin *et al*, in press; Mah *et al*, 1988). Mild epineural and endoneurial perivascular mononuclear inflammation may be observed in up to two-thirds of specimens (De la Monte *et al*, 1988; Griffin *et al*, in press; Lipkin *et al*, 1985; Mah *et al*, 1988). De la Monte and colleagues (1988) characterized these inflammatory cells as T lymphocytes and activated macrophages, with suppressor/cytotoxic cells (CD8) predominating over helper/inducer (CD4) cells endoneurially, and a more equivalent ratio seen epineurally and perineurally. These authors were unable to detect deposition of immunoglobulin, complement, or fibrin by direct immunofluorescence. Several investigators have observed associated demyelination (Bailey *et al*, 1988; De la Monte *et al*, 1988), but this does not appear to be macrophage-mediated or segmental (Bailey *et al*, 1988; Mah *et al*, 1988). In a study comparing autopsy specimens of HIV patients and controls, Bradley and colleagues (1998) found prominent axonal degeneration, segmental demyelination (5% to 6% of nerve fibers), T-cell and macrophage infiltration, and cytokine expression.

Distal axonal degeneration may affect both central and peripheral projections of dorsal root ganglion cells. Rance and colleagues (1988) observed gracile tract degeneration, selective for upper thoracic and cervical segments in 4 of 27 patients with DSP. Loss of dorsal root ganglion cells and mononuclear infiltration is usually mild in comparison to the degree of axonal degeneration and inflammation noted in distal nerves (De la Monte *et al*, 1988; Griffin *et al*, in press; Rance *et al*, 1988).

Although it is not necessary or feasible to obtain sural nerve biopsy specimens in the majority of patients with peripheral neuropathy, epidermal skin biopsy analysis has emerged as a simple, valid, and diagnostically useful test in this population (Herrmann *et al*, 1999). This technique was employed in ACTG Protocol 291, a controlled trial of nerve growth factor in HIV neuropathy, as a quantitative outcome measure of peripheral nerve function (McArthur *et al*, 2000).

Etiology

Although the specific etiology for most cases of DSP in AIDS is unknown, several mechanisms have been proposed. Several authors have reported that HIV infection of peripheral nerve or dorsal root ganglion cells may cause DSP. Ho and colleagues (1985) cultured HIV from sural nerve homogenates in two patients, and HIV from cerebrospinal fluid (CSF) in these two patients and one additional patient. Bailey and colleagues (1988) reported electron microscopic

(EM) evidence of retroviral-like inclusions in myelinated nerve fibers of the sural nerve in one of six patients with DSP. Based on this evidence and the type of mononuclear infiltration suggesting a cell-mediated immune response, De la Monte and colleagues (1988) proposed that peripheral neuropathy in AIDS results from direct HIV infection of peripheral nerve. However, neither of the patients in whom HIV was cultured from sural nerve appears to have had DSP. Other pathologic studies have failed to identify retroviral-like particles or HIV antigens in dorsal root ganglion cells, nerve roots, or peripheral nerves (De la Monte *et al*, 1988; Mah *et al*, 1988; Rance *et al*, 1988), making direct HIV infection of peripheral nerve an unlikely cause of DSP. However, a role for the gp120 subunit of HIV virus has been proposed as a cofactor in the pathogenesis of DSP (Apostolski *et al*, 1993).

Emerging data indicate that plasma HIV viral load is predictive of the occurrence of HIV neuropathy, as is true for neurocognitive disorders. Individuals with plasma HIV RNA levels greater than 10,000 copies/ml have a 2.3-fold greater hazard of sensory neuropathy than those with less than 500 copies/ml (Childs *et al*, 1999). A substudy of ACTG Protocol 291 reveals that HIV viral load is correlated with the severity of HIV neuropathy, as measured by the degree of pain and quantitative sensory test (QST) results (Simpson *et al*, 2002). Aggressive antiretroviral therapy and suppression of plasma HIV-1 viral burden improves sensory function in HIV-infected patients, as measured by quantitative sensory testing (Martin *et al*, 2000). Thus it appears that HIV is linked to the pathogenesis of peripheral neuropathy, although whether this occurs by direct or indirect mechanisms is not clear.

Because HIV may not be principal pathogenetic agent in DSP, research has focused on indirect mechanisms, such as the action of cytokines. Tumor necrosis factor (TNF)-alpha, interleukin-1 (IL-1), and other cytokines have been identified in peripheral nerve (Griffin *et al*, 1993) and dorsal root ganglia (Yoshioka *et al*, 1994) of HIV-infected patients. Griffin and colleagues have suggested that cytokines may interact with nerve growth factors (Griffin *et al*, 1993; Tyor *et al*, 1995). Petratos and colleagues (1999a, 1999b) reported high titers of immunoglobulin (Ig)G and IgM antisulphatide antibodies in a small cohort of HIV-infected patients, suggesting that these may participate in the pathogenesis of HIV neuropathy. Further studies are needed to clarify the role of these agents in the pathogenesis of DSP in AIDS.

Neurotoxic neuropathy

Several drugs used in the treatment of HIV-related complications may cause DSP. A majority of patients with lymphoma or Kaposi's sarcoma that are treated with chemotherapeutic regimens, particularly vincristine, develop symptoms and signs of DSP. Peripheral neuropathy may develop in patients treated with isoniazide (INH) for tuberculosis, particularly when pyridoxine is not supplemented. Thalidomide, which is under investigation in the treatment of HIV-associated aphthous ulcer, may also cause DSP (Ochonisky *et al*, 1994). However, in a controlled study of thalidomide in AIDS-associated oral and esophogeal apthous ulcers, the drug was well tolerated (Jacobson *et al*, 1999).

The nucleoside analogue antiretroviral agents have several dose-limiting toxicities. Although zidovudine (AZT) is limited by hematologic toxicity, there is no evidence that AZT causes DSP (Simpson and Olney, 1992). The dideoxynucleoside analogues didanosine (ddI), zalcitabine (ddC), and stavudine (d4T) have well-recognized neurotoxicity (Simpson and Tagliati, 1995). Unexpected peripheral neuropathy was first described in patients receiving ddC (Dubinsky *et al*, 1989). The neuropathy associated with ddC is clinically and electrophysiologically similar to HIV-related DSP. The most common early symptoms are burning, paresthesias, or aching in the distal lower extremities. Reduced pinprick, temperature, light touch, and vibratory sensation in the lower extremities and absent ankle reflexes are typical in these patients. Electrophysiologic abnormalities are similar to those in HIV-associated DSP, and indicate distal axonopathy (Tagliati *et al*, 1999). The acute onset and rapid progression of nucleoside-related DSP, and particularly the beneficial effect of drug withdrawal, serve to distinguish HIV-associated DSP from nucleoside toxicity (Berger *et al*, 1993; Dubinsky *et al*, 1989).

The occurrence of toxic neuropathy is dose-dependent. In a series of 52 patients receiving four ddC dose regimens, all who received high dose (0.12 to 0.24 mg/kg/day) and 80% of those receiving intermediate dose (0.04 mg/kg/day) developed DSP. Only two of six patients who received low dose ddC (0.02 mg/kg/day) complained of neuropathic symptoms (Berger *et al*, 1993). Furthermore, the onset and clinical characteristics of DSP were substantially different in the three groups. When ddC was withdrawn, patients in the high-dose group experienced a period of "coasting," in which the symptoms of neuropathy intensified for several weeks before improving (Berger *et al*, 1993). The toxic effects of ddC may be reduced by alternating therapy with AZT (Skowron *et al*, 1993). In ACTG Protocol 175, comparing four different treatment regimens (AZT, ddI, AZT/ddI, AZT/ddC), the incidence of DSP was highest in the AZT/ddC arm at 6% (Simpson *et al*, 1998).

Painful DSP is also a common, dose-limiting effect of ddI therapy (Cooley *et al*, 1990; Kieburtz *et al*, 1992; Lambert *et al*, 1990). The varying incidence of neuropathy in different studies may result from different ddI doses and schedules (Cooley *et al*, 1990; Lambert *et al*, 1990). Reversible ddI-related

neuropathy was reported in 10 of 44 (23%) patients followed for at least 10 months. These patients were taking higher daily doses (27.2 mg/kg) and had higher cumulative doses (2.6 g/kg) of ddI than did the patients who remained asymptomatic (13.9 mg/kg/day and 1.75 g/kg). Once the symptoms of peripheral neuropathy had resolved, most patients tolerated rechallenge with ddI at half-dose (Kieburtz *et al*, 1992). A maximum ddI dosage of 12.5 mg/kg/day is recommended by several investigators to avoid the development of neuropathy (Cooley *et al*, 1990; Kieburtz *et al*, 1992; Lambert *et al*, 1990). However, in patients with a low CD4 count, ddI-related neuropathy may develop at lower cumulative doses (Rathburn and Martin, 1992). Furthermore, patients with a previous history of clinical or subclinical neuropathy, older age, and poor nutrition, are more prone to develop ddI-associated DSP (Pike *et al*, 1993; Tagliati *et al*, 1999).

d4T is a later generation nucleoside analogue that may also cause DSP. In a study of 36 patients taking a maximum d4T dose of 2 mg/kg/day, 20 (55%) developed dose-limiting peripheral neuropathy, with clinical features similar to ddC- and ddI-induced DSP (Browne *et al*, 1993). Dose-dependent neuropathic effects of d4T were observed in a randomized trial, comparing doses of 0.5, 1.0, and 2.0 mg/kg/day in 152 patients (median CD4 count = 246 cells/mm^3). DSP occurred in 6%, 15%, and 31% of patients, respectively, with an onset within 8 to 16 weeks of therapy (Bristol Myers Squibb, data on file). In another large ($N = 10{,}348$), blinded randomized study in patients with advanced HIV disease (median CD4 count = 41 cells/mm^3), DSP was reported in 21% of patients receiving 40 mg twice per day (approximately 1.0 mg/kg/day) and in 15% of those receiving 20 mg twice per day (approximately 0.5 mg/kg/day). Patients with a history of neuropathy, low CD4 count, Karnofsky score <80, or hemoglobin level <110 g/dl were at increased risk of developing DSP during d4T treatment (L. Dunkle, Bristol-Myers-Squibb, personal communication). Although early trials of combination ddI/d4T indicate a low incidence of neurotoxicity, these studies were predominantly in early and relatively immunocompetent patients. It might be expected that as combination neurotoxic therapy is employed in more advanced patients with low CD4 counts, the incidence of drug-induced neuropathy will rise. It remains to be determined whether the once daily form of d4T that is currently under development has a similar incidence of toxic neuropathy as the currently available twice-daily preparation.

Hydroxyurea, an adjunctive agent used for control of HIV infection, is neurotoxic, particularly when used in combination with ddI and d4T, as is common in clinical practice. Moore and colleagues (2000) reported data from the Johns Hopkins AIDS Clinic that the combination of ddI, d4T, and hydroxyurea substantially increases the risk of neuropathy over the incidence of neuropathy in patients on ddI monotherapy. Lamivudine (3TC), abacavir, the non-nucleoside reverse transcriptase inhibitors, and the protease inhibitors are not known to be neurotoxic.

The pathogenetic mechanism of toxic neuropathy related to dideoxynucleoside derivatives is unknown. *In vitro* and animal experiments indicate that nucleoside analogues inhibit mitochondrial DNA gamma polymerase (Chen *et al*, 1989). Fialuridine (FIAU), a nucleoside analogue used in clinical trials of hepatitis infection, resulted in several deaths from hepatic and multiorgan toxicity, including lactic acidosis, myopathy, and peripheral neuropathy (McKenzie *et al*, 1995). Histological studies revealed evidence of mitochondrial dysfunction. Numerous clinical toxicities of the antiretroviral nucleoside analogues, including lipodystrophy, have been attributed to mitochondrial toxicity (Brinkman *et al*, 1998), and there have been several case reports reporting lactic acidosis and other features of mitochondrial toxicity in association with nucleoside antiretrovial (ARV) therapy. There have been recent reports of a rapidly progressive neuromuscular weakness syndrome, resembling Guillain-Barré syndrome, associated with lactic acidosis (Marcus *et al*, 2002). Most of these cases have been associated with d4T therapy. However, the experience with AZT and mitochondrial myopathy (Simpson *et al*, 1993) urges caution in accepting such theories until well-controlled trials with adequate control groups clearly separate the effects of the presumed toxic drug from that of HIV or other confounds, which may result in similar clinical syndromes (Lipshultz *et al*, 2000). The author is investigating these issues further in prospective studies.

Carnitine is a critical substrate in mitochondrial metabolism. Fumalaro and colleagues (1997) reported reduced serum levels of acetyl-carnitine in patients with neuropathy related to ddI, ddC, or d4T, which they speculated might interfere with mitochondrial DNA synthesis. This has led to frequent use of carnitine supplementation among patients with HIV- and ARV-related neuropathies. However the number of patients in this study is small, and adequate control groups were not included. In our study of serum carnitine levels in the cohort of patients in ACTG 291, there was no correlation between serum carnitine levels and any measures of severity of HIV or neurotoxic d-drug neuropathy (Simpson *et al*, 2001). Clinical trials of carnitine supplementation for d-drug neuropathy are under development in the ACTG.

Treatment

When a patient with DSP is receiving a known neurotoxin, consideration should be given to reduction in dosage or discontinuation. However,

sometimes maintenance of virological control may be paramount, and a cost-benefit analysis may favor continuation of the neurotoxic antiviral. Although there have been anecdotal reports of DSP improvement with AZT treatment, and one study showed improvement in QST with HAART (Martin *et al*, 2000), further studies are needed to determine whether ARV therapy, with suppression of HIV viral load, leads to clinical improvement in DSP.

The treatment of DSP in HIV-infected individuals is primarily symptomatic. Although there is considerable variability in the treatment of painful neuropathy in current practice, it may be helpful to follow guidelines established by the World Health Organization for the management of cancer pain (World Health Organization, 1990). Using this analgesic ladder as a standard, Breitbart and colleagues (1996) found that 84% of patients with AIDS-related pain syndromes were undertreated for their pain. Numerous barriers related to patient and health care provider behaviors, and the health care system, mitigate against optimal pain relief. The author generally begins with nonopioid analgesics, including nonsteroidal anti-inflammatory agents and acetaminophen. In patients with persistent and more disabling pain, tricyclic antidepressants may afford an added benefit, as has been demonstrated in controlled studies of diabetic neuropathy (Mah *et al*, 1988; Mahieux *et al*, 1989). If these side effects limit dose escalation, tricyclic antidepressants with a lower anticholinergic profile (e.g., nortriptyline, desipramine) may be substituted (Mahieux *et al*, 1989). A controlled study of amitriptyline versus mexiletine (ACTG 242) revealed no significant benefit versus placebo, although the study was prematurely discontinued and may have been underpowered (Kieburtz *et al*, 1998).

Anticonvulsants, such as carbamazepine and phenytoin, may provide symptomatic relief in some patients. Although gabapentin has shown efficacy in the treatment of painful diabetic neuropathy, it has not been subjected to controlled trials in HIV neuropathy. A small, placebo-controlled study revealed that the novel anticonvulant, lamotrigine, effected significant pain reduction in HIV-associated DSP (Simpson, 1994). The author recently reported a large, multicenter study of lamotrigine in painful AIDS neuropathy (Simpson *et al*, 2002). The results indicated significant pain reduction in the subgroup treated with neurotoxic antiretroviral agents. Notably, patients with primary HIV neuropathy, and not receiving neurotoxic ARV, also had substantial pain reduction when treated with lamotrigine. However the large placebo effect in this group negated a significant difference between lamotrigine and placebo in this group.

The use of local anesthetic antiarrhythmics drugs, in particular intravenous lidocaine (Kastrup *et al*, 1987) and oral mexiletine (Dejgard *et al*, 1988), has shown promising results in diabetic painful polyneuropathy. Intravenous lidocaine may be used as a predictor of response to oral mexiletine (Galer, 1994). Topical capsaicin may also be helpful in reducing pain in some patients, although the extent of efficacy of this agent has varied among different controlled studies (Galer, 1994). A small open-label trial of 5% topical lidocaine gel showed encouraging results (Khan *et al*, 1998), and a placebo-controlled trial is under analysis. When disabling pain, refractory to the above agents, are present, narcotics may be required to control symptoms. In these patients, a long-acting opioid agonist, such as methadone or long-acting morphine, may be helpful (Galer, 1994).

In a blinded, placebo-controlled study of 81 patients with DSP, the author found Peptide T to be ineffective in relieving pain, or produce clinical or electrophysiologic improvement of DSP (Simpson *et al*, 1996). Plasmapheresis has not been effective in several patients (Lipkin *et al*, 1985; Miller *et al*, 1988). Many patients with HIV-related conditions, including refractory pain, have tried complementary or alternative therapies. A controlled trial of acupuncture did not reveal significant efficacy in pain reduction as compared to a sham acupuncture control group (Shlay *et al*, 1998). In the first study of a pathogenesis-based agent, recombinant human nerve growth factor (NGF, ACTG 291), was superior to placebo in providing pain reduction in AIDS-associated DSP (McArthur *et al*, 2000). In the 22-week placebo-controlled phase, the only secondary measure of neuropathy that benefited from NGF was pin examination. The results of the 70-week open-label extension of this study revealed similar results (Schifitto *et al*, 2000). Two large phase 3 studies of NGF in the treatment of diabetic neuropathy were negative, prompting the pharmaceutical company to halt further research and development of this drug for any form of neuropathy. There is an urgent need for the study of more effective symptomatic and pathogenesis-based therapies for HIV-associated DSP. Agents currently being developed in clinical trials of HIV neuropathy include L-acetyl-carnitine and prosaptide.

Conclusions

Neuromuscular disorders are common complications of AIDS, although their diagnosis is often delayed. Prompt recognition and early treatment of these disorders are crucial because appropriate therapy may dramatically alter the quality of life and time of survival. Basic research advances in neuro-AIDS will further elucidate pathogenetic mechanisms of these diseases, and should provide a foundation for controlled clinical trials of new therapeutic agents.

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