

Recent advances in HIV neuropathy

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Purpose of review

To describe recent advances in HIV neuropathy.

Recent findings

Epidemiologic studies since highly active antiretroviral therapy was introduced have shown that the incidence of HIV-associated distal sensory polyneuropathy is reduced. Studies have also shown the relationship between distal sensory polyneuropathy and the use of neurotoxic antiretroviral drugs. Skin punch biopsy for assessment of epidermal nerve fiber density is valuable both for diagnosis of distal sensory polyneuropathy and as a predictor of the condition occurring in the future. An in-vitro model of antiretroviral toxic neuropathy showed that dideoxynucleoside analogues that cause neuropathy exert direct mitochondrial toxicity that is not mediated indirectly through the inhibition of DNA polymerase- γ . HIV envelope protein gp120 exerts axonal toxicity directly or indirectly via perineuronal Schwann cells. A feline model of HIV, infection of neonatal cats with the feline immunodeficiency virus, showed development of peripheral neuropathy characterized by loss of epidermal innervation.

Summary

While epidemiological studies of HIV-associated peripheral neuropathy continue to provide useful information, pathogenic studies are moving forward. Animal models of the disease will allow researchers to 'manipulate' the system. It is hoped that these types of studies will translate to an improved understanding of the pathogenesis of HIV-associated neuropathies leading to better treatments.

Keywords

AIDS, HIV, neuropathy, peripheral neuropathy, toxic neuropathy

Introduction

Since this topic was reviewed in *Current Opinion in Neurology* in 2003 [1], several excellent reviews have appeared [2^{••}–4^{••}]. The basic facts concerning the clinical features and classification of HIV-associated neuropathy are well known and have not changed since the original clinical descriptions beginning in the mid-1980s. There are many types of peripheral neuropathies seen in HIV patients (Table 1); only a few appear to be HIV specific, that is they are not seen in other populations. From the earliest reports there appeared to be a link between the type of neuropathy and the stage of HIV infection. The most common peripheral neuropathy in HIV-infected individuals is HIV-associated distal sensory polyneuropathy (DSP). There are two subtypes of DSP: the type solely associated with HIV infection and the type associated with antiretroviral treatments, a toxic polyneuropathy.

Since the introduction of highly active antiretroviral therapy (HAART) in 1996, central nervous system complications of HIV infection have declined dramatically. The incidence and prevalence of peripheral nervous system complications of HIV, however, remain high and may be increasing.

This review concerns developments since the last *Current Opinion in Neurology* review in 2003 and is divided into clinical, research, and treatment sections.

Clinical update

Many recent papers concern epidemiology, which has taken on a new dimension since the introduction of HAART therapy. In general, the recurring theme of risk factor analysis for the development of DSP is the use of neurotoxic antiretroviral drugs.

Hulgan and colleagues [5[•]] performed a long-term case control study within the AIDS Clinical Trial Group (ACTG) Study 384. In the 3-year follow-up, DSP was based on symptoms and signs. In the 509 patients, mitochondrial haplogroup T was more frequent in those who developed neuropathy, as was the receipt of didanosine plus stavudine and older age. A confirmatory study is needed to assess these potentially important results as this may provide a window into risk assessment.

Schifitto and coworkers [6] in the Northeast AIDS Dementia (NEAD) Consortium evaluated the association between markers of immune activation, HIV

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Abbreviations

DRG	dorsal root ganglion
DSP	distal sensory polyneuropathy
HAART	highly active antiretroviral therapy
NRTI	nucleoside reverse transcriptase inhibitor

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Table 1 Peripheral neuropathies associated with HIV infection

HIV-associated sensory neuropathies
Distal symmetric polyneuropathy
Antiretroviral toxic neuropathy
Inflammatory polyneuropathies
Acute inflammatory demyelinating polyneuropathy
Chronic inflammatory demyelinating polyneuropathy
Mononeuritis multiplex
Autonomic neuropathy
Neuropathy in diffuse infiltrative lymphomatosis syndrome
Neuropathies due to opportunistic infections

RNA levels (viral load) and the time to symptomatic DSP. In the cohort, 62.5% did not have symptomatic neuropathy at baseline. The only marker associated with the time to symptomatic neuropathy was macrophage colony stimulating factor (M-CSF) levels as measured in the cerebrospinal fluid, but this was a weak association with a P value = 0.05 among the many items evaluated. More interestingly, the Kaplan-Meier estimate of the 1-year incidence of symptomatic neuropathy was 21%. This can be compared to a prior study by this same group in which the incidence was 36% in the first year. The difference between the current cohort and the prior one was the introduction of HAART therapy. This suggests that HAART therapy is changing the natural history of HIV-associated symptomatic DSP. In addition, the prevalence of DSP continues to rise as patients with HIV infection are living longer.

In contrast, a Spanish group [7] performed a prospective study of neuropathy in patients who had been on HAART treatment for at least 2 years. Starting with those without neuropathy as confirmed by clinical and electrophysiologic findings, only two cases of symptomatic neuropathy were found in the 108 patients (1.8%). Subclinical or asymptomatic neuropathy was found in 66%. While the differences between this study and the American study above may be explained by the differences in symptom reporting, it would be important to explore other variations in the two patient populations as the results differ considerably.

Cherry and coworkers [8[•]] studied a cohort of 147 patients at two international sites to examine the association of risk factors for the involvement of HIV-associated neuropathies. A large number of factors were assessed. Those statistically associated with a heightened risk for symptomatic DSP in the multivariate analysis included only exposure to stavudine and didanosine. Other factors significant in univariate analysis included age and CD4 count. Plasma HIV RNA levels, hepatitis C virus infection, CD4 cell count, B12 levels, HbA1C, race and sex were not associated with symptomatic neuropathy.

In this study also, laboratory data were evaluated for diagnostic efficiency for DSP. Reduced vibratory

thresholds and reduced epidermal nerve fiber density together improved diagnostic efficiency.

Herrmann and colleagues [9[•]] evaluated the use of skin biopsies to predict transition from HIV infection and no neuropathy or asymptomatic DSP to symptomatic DSP. On multivariate analysis, the presence of a low epidermal nerve fiber density (<11 fibers/mm) as assessed by skin biopsy increased the likelihood of developing symptomatic DSP in the following 6–12 months. Unfortunately, nerve conduction studies, a more widely available test, were not performed. The results of this study are in line with many prior studies, in particular of toxic neuropathy, in which clinical examination and, more importantly, nerve conduction studies can predict the development of neuropathy.

While the question of neuropathy in those coinfecting with HIV and hepatitis C remains important, there have been no systematic studies of this.

Pettersen and coworkers [10[•]] examined the clinical and laboratory features and treatment exposures in patients with symptomatic HIV-associated DSP. In their study, patients with HIV neuropathy were older, had higher peak plasma viral loads, exposure to didanosine drugs and protease inhibitors. This is one of two studies showing the effect of protease inhibitors as a risk factor (see below), something that could be easily examined by other existing cohorts.

Lichtenstein and the HIV Outpatient Study Investigators [11] examined retrospectively the risk factors associated with the development of DSP in the HAART era. Using a large provider database and a clinical diagnosis of DSP, only 13% of the cohort were diagnosed with DSP. Risk factors for DSP were age over 40, presence of diabetes, white race, nadir CD4 count of less than 50 cells/mm³, CD4 count of 50–199 cells/mm³, and initial viral load greater than 10 000/ml. While the initial use of didanosine, stavudine, nevirapine, or a protease inhibitor was associated with DSP, the strength of the association decreased over time.

Update on mechanisms

Advances have been made in delineating how HIV proteins indirectly cause axonal or neuronal injury, since direct infection of the neurons by HIV-1 is not likely to be an important mechanism as evidence of direct infection is very limited [12].

Keswani and colleagues [13] showed that HIV-1 envelope protein gp120 could induce indirect neuronal injury through the Schwann cells. When dorsal root ganglion (DRG) sensory neurons and Schwann cells, in a coculture paradigm, were exposed to chemokine

receptor CXCR4, tropic gp120, or (monogamous CXCR4 ligand stromal-derived factor) (SDF-1 α), there was an upregulation of RANTES (regulated upon activation, normal T-cell expressed and secreted) by the Schwann cells through the chemokine receptor CXCR4. Schwann cell secreted RANTES bound to the chemokine receptor CCR5 on the neurons and induced upregulation of tumor necrosis factor- α (TNF- α) in neurons. This upregulation of TNF- α resulted in a classical apoptotic neuronal death in sensory neurons. Axonal degeneration was partially blocked by a specific caspase inhibitor, but it was not clear if this effect was a direct action on the mechanism underlying axonal degeneration or it was an indirect effect due to the apoptotic death of the neuronal body.

One of the hallmarks of many peripheral neuropathies is distal axonal degeneration without significant cell death at the neuronal level. Most studies directed at neuronal toxicity or degeneration are focused on events that are occurring at the cell body level, but local axonal mechanisms may play a bigger role in mediating distal axonal degeneration and they may be distinct from the intracellular events at the cell body [14]. Melli and coworkers [15^{••}] took advantage of a compartmentalized culture system to ask questions specific for the cell body versus the axon. In this in-vitro cell culture method, one can isolate the neuronal cell body from the axonal compartment and manipulate each individually. Furthermore, one can examine the role of perineuronal and periaxonal Schwann cells individually as these cells can be added or removed from each compartment. As in the previous study, perineuronal Schwann cells were responsible for mediating an apoptotic neuronal toxicity of gp120 on the cell body; axonal degeneration was secondary to the cell death. This was in contrast to the mechanism of toxicity of gp120 on the axon and the role periaxonal Schwann cells played in this axonal toxicity. When applied directly onto axons, gp120 bound to chemokine receptors and induced axonal degeneration that was preventable by the chemokine receptors. Furthermore, this process was dependent upon the activation of the caspase pathway independent of the neuronal cell body. Periaxonal Schwann cells did not mediate this direct axonal toxicity and in fact played a partial neuroprotective role. This 'neuroprotective' role for periaxonal Schwann cells may be a common theme for other injury models in the peripheral nervous system [16].

Although, these in-vitro studies shed some light onto potential mechanisms of HIV-induced axonal degeneration, many unanswered questions remain. For example, how does binding of gp120 onto the chemokine receptors lead to the activation of the caspase pathway and distal axonal degeneration? Which intracellular signaling pathways are involved? Do these pathways share common key elements with other causes of peripheral neuropathies?

One potential answer comes from a study by Bodner and colleagues [17], who observed that CEP-1347, an inhibitor of the mixed lineage kinases, prevented the neuronal apoptosis induced by gp120 as well as the neuronal death caused by a nucleoside reverse transcriptase inhibitor (NRTI), didanosine. Both gp120 and didanosine activated the c-Jun N-terminal kinase pathway and caused death of DRG neurons. The investigators, however, did not examine axonal degeneration and it is unclear whether the observation regarding the sensory neuronal death *in vitro* could be generalized to the in-vivo situation, with very limited death in the DRG.

Furthermore, induction of apoptosis reported in this study is in contrast to another previous study in which the NRTIs cause axonal degeneration and nonapoptotic cell death in DRG sensory neurons [18]. For many years, antiretroviral toxic neuropathy has been attributed to mitochondrial toxicity due to inhibition of the mitochondrial DNA polymerase- γ . Several lines of evidence, however, argue against this as the sole mechanism of NRTI neurotoxicity [2^{••}]. For example, zidovudine is a potent inhibitor of mitochondrial DNA polymerase- γ but does not cause neuropathy in HIV patients. Second, exposure to NRTIs correlates with mitochondrial DNA content in the subcutaneous fat biopsies but not to the incidence or severity of neuropathy [19]. In their in-vitro study, Keswani and colleagues [18] showed that NRTIs that cause neuropathy in HIV patients cause direct mitochondrial toxicity through inhibition of the mitochondrial transmembrane potential differential. This leads to energy failure and subsequent axonal degeneration and nonapoptotic cell death in DRG sensory neurons. This effect is not preventable by a specific caspase inhibitor, suggesting that the classical apoptotic pathway is not involved in NRTI neurotoxicity. Nevertheless, further studies using in-vivo models of HIV-induced peripheral neuropathies will be needed to examine the full biological relevance of these in-vitro observations.

Although small rodent models of HIV-associated sensory neuropathies are in development (C. Jack, C. Zhou and A. Hoke, unpublished observations), in 2004 Kennedy and colleagues [20] reported development of another lentiviral-induced neuropathy in cats. Infection of neonatal cats with the feline immunodeficiency virus (FIV) resulted in macrophage infiltration of the DRG and the peripheral nerves associated with reduction in epidermal sensory nerve density. The exact mechanisms underlying this axonal degeneration remain to be determined but recent papers by the same group [21[•],22[•]] suggest that both macrophages and CD8⁺ lymphocytes play important roles in mediating an indirect neurotoxicity. Exposure of cat DRG neurons to FIV-infected macrophages resulted in axonal degeneration and neuronal atrophy and death [22[•]]. This effect was mediated

through the activation of the inducible nitric oxide synthase in the infected macrophages. In addition to the macrophages, lymphocyte infiltration of the DRG has been observed in human autopsy specimens [23]. The role of lymphocytes in mediating neuropathy in HIV infection, however, had not been studied in detail. Zhu and colleagues [21•] observed that cats infected with the FIV exhibited an increase in the number of CD8+ lymphocytes in the DRG and the peripheral nerves. Taking their in-vivo observations to the in-vitro co-culture system, they showed that FIV-infected CD8+ lymphocytes could cause axonal degeneration and neuronal death that required cell–cell contact and interaction of CD40 on DRG neurons and CD154 on lymphocytes. These important studies provide an insight into potential mechanisms in FIV-induced neuropathy in cats, but further studies will be needed to corroborate the role of these observations in HIV-associated sensory neuropathies.

Treatment

Treatment trials of symptoms of painful HIV DSP continue to be important. One recent paper estimated that 1 year of treatment of painful peripheral neuropathy cost US\$17 000 per person per year in the US [24]. Clinical trials in HIV-associated DSP have interestingly shown that the results of treatment trials in painful diabetic neuropathy, the industry standard, cannot just be superimposed on those with HIV-associated painful DSP.

The Lidoderm-HIV Neuropathy Group [25] showed that lidocaine 5% gel was ineffective in the treatment of pain associated with HIV DSP.

In contrast, a placebo-controlled trial of gabapentin published by the German Neuro-AIDS Working Group [26] using a relatively standard approach showed an effect on pain scores. The study population, however, included only 26 individuals of whom only 21 completed the entire 7-week study. A large study is needed to confirm this finding.

Two treatment studies have been performed using acetyl-L-carnitine [27,28]. Unfortunately, neither study included controls. Both showed positive results: the Herzmann study an affect on neuropathy *per se* [27] and the Osio study on pain [28]. It may be appropriate to perform further placebo-controlled studies of this compound which has a known safety profile.

Conclusion

While epidemiological studies of HIV-associated peripheral neuropathy continue to provide useful information, pathogenic studies are finally moving forward. The development of animal models of the disease will allow researchers to ‘manipulate’ the system. It

is hoped that these types of studies will translate into better understanding of the pathogenesis of HIV-associated neuropathies.

References and recommended reading

- Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
 - of outstanding interest
- Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 487–489).
- 1 Luciano CA, Pardo CA, McArthur JC. Recent developments in the HIV neuropathies. *Curr Opin Neurol* 2003; 16:403–409.
 - 2 Hoke A, Cornblath DR. Peripheral neuropathies in human immunodeficiency virus infection. In: Dyck PJ, Thomas PK, editors. *Peripheral neuropathy*, 4th ed Philadelphia, PA: Elsevier; 2005. pp. 2129–2145.
An excellent review of the entire subject.
 - 3 McArthur JC, Brew BJ, Nath A. Neurological complications of HIV infection. *Lancet Neurol* 2005; 4:543–555.
An excellent review of the entire subject.
 - 4 Ferrari S, Vento S, Monoco S, *et al.* Human immunodeficiency virus-associated peripheral neuropathies. *Mayo Clinic Proc* 2006; 81:213–219.
An excellent more clinically based review of the entire subject.
 - 5 Hulgan T, Haas DW, Haines JL, *et al.* Mitochondrial haplogroups and peripheral neuropathy during antiretroviral therapy: an adult AIDS clinical trials group study. *AIDS* 2005; 19:1341–1349.
The paper suggests that mitochondrial haplogroup T was more frequent in those developing neuropathy which could be tested in other cohorts and may provide insights into pathogenesis.
 - 6 Schifitto G, McDermott MP, McArthur JC, *et al.* Markers of immune activation and viral load in HIV-associated sensory neuropathy. *Neurol* 2005; 64:842–848.
 - 7 Villela-beitia-Jaureguizar K, Rivas-Gonzalez P, Ibarra-Luzar JI, *et al.* Clinical and subclinical neuropathy in patients with human immunodeficiency virus receiving antiretroviral therapy. *Rev Neurol* 2006; 42:513–520.
 - 8 Cherry CL, Skolasky RL, Lal L, *et al.* Antiretroviral use and other risks for HIV-associated neuropathies in an international cohort. *Neurology* 2006; 66:867–873.
A multinational epidemiological study concluding that antiretroviral drug exposure plays a significant role in development of DSP.
 - 9 Herrmann DN, McDermott MP, Sowden JE, *et al.* Is skin biopsy a predictor of transition to symptomatic HIV neuropathy? A longitudinal study. *Neurology* 2006; 66:857–861.
A multicenter study showing that punch skin biopsies can predict the transition from HIV infection and no neuropathy or asymptomatic DSP to symptomatic DSP.
 - 10 Pettersen JA, Jones G, Worthington C, *et al.* Sensory neuropathy in human immunodeficiency virus/acquired immunodeficiency syndrome patients: protease inhibitor-mediated neurotoxicity. *Ann Neurol* 2006; 59:816–824.
This is one of two studies showing that exposure to protease inhibitors is a risk factor for development of DSP.
 - 11 Lichtenstein KA, Armon C, Baron A, *et al.* Modification of the incidence of drug-associated symmetrical peripheral neuropathy by host and disease factors in the HIV outpatient study cohort. *Clin Infect Dis* 2005; 40:148–157.
 - 12 Pardo CA, McArthur JC, Griffin JW. HIV neuropathy: insights in the pathology of HIV peripheral nerve disease. *J Peripher Nerv Syst* 2001; 6:21–27.
 - 13 Keswani SC, Polley M, Pardo CA, *et al.* Schwann cell chemokine receptors mediate HIV-1 gp120 toxicity to sensory neurons. *Ann Neurol* 2003; 54:287–296.
 - 14 Hoke A. Neuroprotection in the peripheral nervous system: rationale for more effective therapies. *Arch Neurol* (in press).
 - 15 Melli G, Keswani SC, Fischer A, *et al.* Spatially distinct and functionally independent mechanisms of axonal degeneration in a model of HIV-associated sensory neuropathy. *Brain* 2006; 129:1330–1338.
Using a unique compartmentalized culture system, the authors showed that gp120 could cause axonal degeneration when applied directly on the axon and lead to neuronal toxicity via Schwann cells when applied on the neuronal cell body. This study points to the complexity of mechanisms of toxicity and shows that distal axonal degeneration may have distinct mechanisms from neuronal injury at the cell body level.
 - 16 Keswani SC, Buldanlioglu U, Fischer A, *et al.* A novel endogenous erythropoietin mediated pathway prevents axonal degeneration. *Ann Neurol* 2004; 56:815–826.

- 17 Bodner A, Toth PT, Miller RJ. Activation of c-Jun N-terminal kinase mediates gp120III_B- and nucleoside analogue-induced sensory neuron toxicity. *Exp Neurol* 2004; 188:246–253.
- 18 Keswani SC, Chander B, Hasan C, *et al*. FK506 is neuroprotective in a model of antiretroviral toxic neuropathy. *Ann Neurol* 2003; 53:57–64.
- 19 Cherry CL, Gahan ME, McArthur JC, *et al*. Exposure to dideoxynucleosides is reflected in lowered mitochondrial DNA in subcutaneous fat. *J Acquir Immune Defic Syndr* 2002; 30:271–277.
- 20 Kennedy JM, Hoke A, Zhu Y, *et al*. Peripheral neuropathy in lentivirus infection: evidence of inflammation and axonal injury. *AIDS* 2004; 18:1241–1250.
- 21 Zhu Y, Antony J, Liu S, Martinez JA, *et al*. CD8⁺ lymphocyte-mediated injury of dorsal root ganglion neurons during lentivirus infection: CD154-dependent cell contact neurotoxicity. *J Neurosci* 2006; 26:3396–3403.
- FIV-infected lymphocytes caused axonal degeneration in sensory neurons.
- 22 Zhu Y, Jones G, Tsutsui S, *et al*. Lentivirus infection causes neuroinflammation and neuronal injury in dorsal root ganglia: pathogenic effects of STAT-1 and inducible nitric oxide synthase. *J Immunol* 2005; 175:1118–1126.
- FIV-infected macrophages caused neuronal toxicity that was mediated through nitric oxide.
- 23 Esiri MM, Morris CS, Millard PR. Sensory and sympathetic ganglia in HIV-1 infection: immunocytochemical demonstration of HIV-1 viral antigens, increased MHC class II antigen expression and mild reactive inflammation. *J Neurol Sci* 1993; 114:178–187.
- 24 Berger A, Dukes EM, Oster G. Clinical characteristics and economic costs of patients with painful peripheral neuropathic disorders. *J Pain* 2004; 5:143–149.
- 25 Estanislao L, Carter K, McArthur JC, *et al*. A randomized controlled trial of 5% lidocaine gel for HIV-associated distal symmetric polyneuropathy. *J Acquir Immune Defic Syndr* 2004; 37:1584–1586.
- 26 Hahn K, Arendt G, Braun JS, *et al*. A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies. *J Neurol* 2004; 251:1260–1266.
- 27 Herzmann C, Johnson MA, Youle M. Long-term effect of acetyl-L-carnitine for antiretroviral toxic neuropathy. *HIV Clin Trials* 2005; 6:344–350.
- 28 Osio M, Muscia1 F, Zampini M, *et al*. Acetyl-L-carnitine in the treatment of painful antiretroviral toxic neuropathy in human immunodeficiency virus patients: an open label study. *J Periph Nerv Sys* 2006; 11:72–76.