

Recent developments in the HIV neuropathies

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Purpose of review

With the introduction of highly active antiretroviral therapy peripheral neuropathies have become the most common neurological complications in HIV infection. The frequency and spectrum of these neuropathies are changing, as the various toxic and immune factors are modified by new treatment strategies. Recent studies have provided a better understanding of the risk factors, markers and relevant pathogenic mechanisms, and a thorough review of these is critical for an improved understanding of this important and increasingly common complication.

Recent findings

The combined use of dideoxynucleosides, in association with immune-mediated mechanisms triggered by HIV infection, are critical in the development of distal sensory polyneuropathy. Valuable markers of neuropathy such as intraepidermal nerve fiber density from skin biopsies have been validated and promise to be a valuable tool in the detection and monitoring of distal sensory polyneuropathy. Markers of virological activity have also been associated with the severity of neuropathic pain in distal sensory polyneuropathy. In some instances, the enhanced viral suppression from antiretroviral agents may actually improve or decrease the frequency of certain types of neuropathy. New evidence supports mitochondrial toxicity as a principal mechanism for dideoxynucleoside-associated sensory neuropathy, and questions arise about enhanced risk with pre-existing mitochondrial defects. Confirmed treatments are limited to the reduction of symptoms, with a need for the further investigation of corrective therapies.

Summary

Increased and improved surveillance for HIV-associated neuropathy will allow earlier interventions to improve quality of life and prevent severe toxicities. A better understanding of the prevailing mechanisms will allow for more effective interventions.

Keywords

distal sensory polyneuropathy, HIV-1, immune-mediated neuropathy, mitochondrial toxicity, peripheral neuropathy, toxic neuropathy

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Abbreviations

DSP	distal sensory polyneuropathy
GBS	Guillain-Barré syndrome
HAART	highly active antiretroviral therapy
HTLV	human T-cell lymphotropic virus
IENF	intraepidermal nerve fiber
NGF	nerve growth factor

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Introduction

The combination of improved HIV suppression, the use of highly active antiretroviral therapy (HAART), and increased survival with prolonged medication exposure, has resulted in complex interactions between all these factors and the risk of neuropathy. It is known that distal sensory polyneuropathy (DSP) occurs in approximately a third of all HIV-infected patients, and is the most common form of neuropathy in HIV [1•]. Although the pathogenesis of DSP remains unclear, evidence to date indicates that the two prevalent mechanisms are immunological dysfunction secondary to HIV [2•], and the neurotoxic effects of antiretroviral drugs (particularly dideoxynucleosides) [3,4•]. However, there are still many outstanding questions regarding frequency, risk factors, mechanisms and potential interactions with other coexistent conditions. This review will examine the most recent information on the HIV-associated neuropathies in the HAART era.

Epidemiology

Although the incidence of DSP has decreased, the incidence of antiretroviral drug-induced toxic neuropathy has increased [5••]. A recent study of 252 patients enrolled in a pre-HAART trial of HIV-infected individuals at high risk of complications, found a prevalence rate of 20% for asymptomatic neuropathy and 35% for symptomatic neuropathy [6••]. The estimated one year incidence rate of symptomatic distal sensory neuropathy was 36%, and for both asymptomatic or symptomatic neuropathy it was 52%. That study provided important information: (1) that DSP is a very common complication in HIV infection, even before the use of HAART; (2) that subclinical asymptomatic neuropathy is more frequent than generally thought; (3) that asymptomatic DSP did not increase the risk of symptomatic DSP and, as proposed by the authors, may suggest that the two are different entities and not really part of a continuum; and (4) that seemingly unrelated markers such as mood are significantly associated with neuropathy, implying that neuropathy could be a reflection of nervous system

dysfunction, as a whole. The main limitation of the study is that it was performed before the introduction of HAART, and the figures do not reflect the increased risk from combined antiretroviral use now encountered.

The number of older individuals with HIV infection and AIDS is expected to rise both from the impact of HAART and prolonged survival, and from de-novo infection in the elderly population. A recent article reviewing the impact of aging in HIV infection and its neurological complications [7•] explained that aging is associated with a higher viral load and immunosenescence, with a decrease in the naive subsets of CD4 cells, decreases in T cell proliferative responses and decreased ability to respond to novel pathogens, resulting in a potential synergism between HIV-1 infection and aging. In addition, the presence of co-morbid conditions associated with the increased risk of neuropathy, and more common with advancing age, will impact the frequency of neuropathy in this population.

Peripheral neuropathy in HIV infection may occur as a result of the primary HIV infection or from exposure to neurotoxic antiretroviral agents, in particular from the dideoxynucleosides, zalcitabine, didanosine and stavudine [1•]. The combined use of dideoxynucleosides, as often used in HAART, has been shown to be synergistic in its neurotoxic effects, and increases the risk of neuropathy substantially [3]. Two recent studies have provided additional information about the risk of developing dideoxynucleoside-associated polyneuropathy. The frequency of neuropathy was examined in a post-hoc analysis of safety data from 86 zidovudine-naïve patients in a protocol that evaluated the characteristics of HIV-1 isolates from poor responders to stavudine-containing regimens [8•]. They found an incidence of neuropathy of 21% and, in agreement with previous studies, an increased incidence with an increased number of drugs and with longer exposure. The results, however, were not adjusted for other risk factors for neuropathy and were somewhat limited by the lack of a systematic assessment for dideoxynucleoside-associated polyneuropathy. Another study examined the frequency of incident neuropathy in a 6 month trial of combined stavudine and didanosine therapy, both associated with toxic neuropathy [9]. Contrary to the aforementioned studies, they only found a modest increase in incident neuropathy, which they reported at 12%. This figure may have been influenced by the short duration of the study or by the fact that the methodology used to detect neuropathy was not uniform among all subjects, and the results were not adjusted for other risk factors.

Pathogenesis

It is known that DSP becomes more prevalent with advanced immunosuppression and increased viral repli-

cation, but can also increase with the use of combined dideoxynucleoside therapy through its neurotoxic effects, even in the presence of improved viral suppression [1•]. These two seemingly opposed possibilities raise important questions in the era of HAART: which mechanism will be more influential in the development of neuropathy, the improved viral suppression or the increased neurotoxin exposure? At least one previous study [10] showed an improvement in the physiological measures of neuropathy in patients who responded to antiretroviral therapy, in spite of increased exposure to neurotoxic medications. Two recent case reports present findings that may suggest a therapeutic effect from HAART in Guillain-Barré syndrome (GBS), in one case with concomitant anti-cytomegalovirus therapy. One antiretroviral-naïve patient with acute GBS and advanced HIV infection appeared to improve after the introduction of HAART, with an improvement in viremia and CD4 cell measures [11•]. Although only a single case and confounded by the self-limited nature of GBS, the report raised the possibility of a direct effect of improved viral suppression with HAART and a potential effect of viral replication in this demyelinating neuropathy. An additional report of an antiretroviral-naïve patient with evidence of advanced HIV-1 infection and with GBS associated with acute cytomegalovirus infection [12], showed a dramatic recovery after the concomitant use of HAART and ganciclovir. The report raised important questions about the need to check for concomitant cytomegalovirus infection in HIV-1-infected patients with a picture of GBS, and the potential benefit from anti-cytomegalovirus therapy. Both cases show that GBS may occur in advanced stages, and is not limited to the time of seroconversion or the early stages.

An additional case report presented an opposite effect from HAART and improved viral suppression [13]. An antiretroviral-naïve patient developed a relapse of a demyelinating polyneuropathy (probably chronic inflammatory demyelinating polyradiculoneuropathy) after treatment with HAART and a rapid recovery of immune parameters. The authors argued that the relapse was the result of the improved viral suppression with immune reconstitution. Although difficult to prove, the coincidental and vigorous increase in CD4 lymphocytes supported a very provocative argument.

One important aspect that has arisen with the use of dideoxynucleosides relates to the possibility of a stavudine-associated, rapidly ascending syndrome of neuromuscular weakness and respiratory failure, mimicking GBS [14]. The syndrome may be associated with hyperlactatemia and is currently under investigation. An interesting possibility of the coincidental development of a GBS-like, rapidly progressive motor neuropathy with exposure to a dideoxynucleoside has recently been

reported [15]. The patient, a woman undergoing treatment for human T-cell lymphotropic virus (HTLV) type 1-associated leukemia with zidovudine, developed a rapidly progressive motor neuropathy that progressed to quadriplegia and required mechanical ventilation. This was associated with lactic acidosis and markedly increased levels of coproporphyrin. On the basis of this, the authors suggested that dideoxynucleosides may precipitate acute porphyric neuropathy in patients with underlying disturbances of porphyrin metabolism, or less likely, that they can produce disturbances in porphyrin metabolism and secondary porphyric neuropathy.

What is the mechanism of dideoxynucleoside-associated neuropathy? Although the precise cause is not known, there is abundant indirect evidence of mitochondrial dysfunction as a principal mechanism. One possibility that had been reported earlier [16] was a deficiency in serum levels of acetyl-carnitine, a critical substrate for normal mitochondrial function. This has been challenged by the results from a recent study of a much larger sample of patients who participated in the nerve growth factor (NGF) trial [17•]. Comparing patients with dideoxynucleoside-associated polyneuropathy and primary (non-dideoxynucleoside) HIV neuropathy, the investigators failed to observe a significant difference in total, free carnitine, or acetyl carnitine between the two groups, or an association with other clinical and physiological markers of neuropathy. Dalakas and colleagues [18••] provided direct, pathological evidence of mitochondrial abnormalities in sensory nerves of patients with zalcitabine-induced neuropathy. Using quantitative methods and sural nerve specimens from four HIV-infected patients with zalcitabine-associated neuropathy, they were able to demonstrate an increased number of abnormal mitochondria in the axons and Schwann cells, as well as mitochondrial DNA depletion. Sural nerve specimens from zalcitabine-naïve HIV-1-infected patients and non-HIV neuropathy patients, showed a much smaller number of abnormal mitochondria and no evidence of mtDNA depletion. The paper provided further compelling evidence of mitochondrial damage as the cause of dideoxynucleoside-associated neuropathy. This mitochondrial dysfunction is attributed to the inhibition of DNA polymerase gamma, the enzyme responsible for mtDNA replication. One possible mechanism to explain the enhanced susceptibility for toxic neuropathy in some but not all individuals exposed to dideoxynucleosides could be genetic variations in the polymerase gamma. Chen and colleagues [19••] investigated whether CAG repeat expansions or mutations in the DNA polymerase gamma gene explained this susceptibility. They were unable to find any correlations between CAG repeat expansions and the presence of neuropathy or mutations in the coding regions and lactic acidosis. The study was one of

a few examining specific mechanisms that could explain the differences or increased susceptibility from a superimposed, genetically encoded variant. This possibility of enhanced susceptibility to antiretroviral toxicity in the context of an underlying mitochondrial defect has also been proposed in some recent reports of HIV-1-infected patients with the mitochondrial mutation of Leber hereditary optic neuropathy, with new onset or worsening visual symptoms after receiving treatment with antiretroviral agents [20–22].

How can one monitor or detect mitochondrial toxicity in early or presymptomatic stages? Cherry *et al.* [23••] reported an improved method to measure mtDNA from subcutaneous fat samples obtained from skin biopsies. In a group of 60 patients enrolled in a study of DSP, 50% of whom had clinical neuropathy, a significant correlation was shown between reduced mtDNA in subcutaneous fat and exposure to nucleoside reverse transcriptase inhibitors. The reduction was more prominent with exposure to dideoxynucleosides, but, interestingly, as a cross-sectional measurement it did not correlate with the presence of neuropathy or lipoatrophy. This may prove to be a valuable method to detect mitochondrial toxicity in pre-symptomatic stages, or alternatively a way to monitor for mitochondrial toxicity in patients exposed to antiretroviral drugs.

One important aspect in the study of the risks of peripheral neuropathy in HIV-1 infection is the role of coexistent infections acquired through high-risk behaviour or as a result of impaired immunocompetence. A recent study [24••] examined the frequency of HTLV-2 co-infection and its role in the progression of AIDS and the development of neurological complications, including peripheral neuropathy. HTLV-2 infection has been identified in intravenous drug users, and may sometimes result in a myelopathy, similar to that reported with HTLV-1 infection (tropical spastic paraparesis). In that study of over 1000 HIV-1-infected patients, the authors reported a prevalence of co-infection of 8.2%, and they followed 30 of the patients for 28.5 months. They reported an incidence of neuropathy of 40% during the observation period, with a significantly higher, time-dependent probability of developing peripheral neuropathy (hazard ratio of 3.3). Contrary to other studies, the higher risk of neuropathy was not associated with worse parameters for HIV progression, which did not change. Despite the lack of a significant correlation with HIV immune parameters, the risk of peripheral neuropathy for both co-infected and singly infected patients decreased after receiving HAART. Although the interaction is not clear, this suggests that peripheral neuropathy may develop as a result of co-infection with other neurotropic infectious agents, independent of its effect on the primary HIV infection. If HIV-associated immune

parameters did not correlate with the risk of peripheral neuropathy in this cohort, then it is not clear how the introduction of HAART reduced the risk of neuropathy. Other possibilities, such as a direct effect of HAART on HTLV-2, or other mechanisms not associated with immunocompetence, were not explored.

Although infrequent, vasculitic neuropathy is known to occur in HIV-infected patients. In the immunocompromised host these may be associated with infections by cytomegalovirus or varicella zoster virus. A recent paper from the Indian continent [25] described four cases of patients with vasculitic neuropathies as the presenting manifestation of HIV infection. All patients showed elevated sedimentation rates without evidence of other rheumatological conditions. Clinically, the presentation was that of an asymmetric sensorimotor, predominantly axonal, polyneuropathy with additional facial nerve involvement in some cases. Varying degrees of vasculitic changes were described in the sural nerve specimens, without evidence of cytomegalovirus or HIV invasion by immunostaining. That study recognized this type of neuropathy as an initial presentation of HIV-1 infection, and reinforced the value of histological and serological examinations in atypical or unexplained neuropathies.

Can dideoxynucleosides aggravate a pre-existing motor neuropathy? In a recent isolated report of a patient with Charcot–Marie–Tooth type 1A [26], a predominantly motor inherited demyelinating neuropathy, the authors suggested that the absence of a worsening of motor parameters indicated that dideoxynucleosides did not aggravate the pre-existing neuropathy. Although an interesting argument, the rapid onset of ‘intense paraesthesias’ that the authors described could be construed as evidence of aggravation, because Charcot–Marie–Tooth type 1A affects both motor and sensory axons, and because dideoxynucleosides preferentially affect sensory neurons. An additional report [27] underscored the need to consider the possibility of a coexistent inherited neuropathy in patients with HIV-associated neuropathies.

Markers of severity

The diagnosis of the HIV-associated peripheral neuropathies still relies on a careful clinical and electrodiagnostic examination. In DSP, however, there is prominent involvement of small myelinated and unmyelinated fibers, and these are difficult to evaluate clinically or electrodiagnostically. Skin biopsies with nerve fiber density evaluation have been shown to be of value in the assessment of peripheral neuropathies with prominent involvement of small fibers, including DSP [28,29]. A report by Polidefkis *et al.* [30**] provided additional important information on DSP. An analysis of intraepidermal nerve fiber (IENF) densities from skin biopsies

obtained from 60 subjects enrolled in the NGF trial in HIV sensory neuropathy study [31] revealed that IENF density was significantly and inversely correlated with some measurements of neuropathic pain. IENF densities were also associated with measures of HIV activity, specifically lower CD4 cell counts and higher plasma HIV-RNA levels. Contrary to what would be expected, the study showed a significant correlation with vibratory perception thresholds in the toe (a large fiber modality), but not with cold perception thresholds (a small fiber modality). Overall, the study provided additional important information that helped validate this novel technique as an added measure of severity of neuropathy and as a reflection of the influence of viral replication in DSP. The good reproducibility would suggest added value as an outcome measure, but the time course of epidermal reinnervation may limit its value in short-term clinical trials.

Previous studies have shown that increased viral replication, with resultant high viral loads and low CD4 cell counts, is a risk factor for prevalent and incident DSP. However, a more direct association with the severity of DSP was not clear. A recent post-hoc analysis of data from the NGF trial [32*] has shown a modest but significant correlation between HIV-RNA levels and the severity of neuropathic pain caused by DSP, as measured by scores of magnitude of neuropathic pain. The association with other objective measurements of nerve function such as quantitative sensory testing was not as clear. However, these results add important information to the relation between HIV viremia and DSP, and suggest a more intimate relationship between viral replication and neuropathy symptoms. Could the association of the severity of neuropathic pain with high viral replication suggest a role of viral by-products in painful DSP? HIV envelope glycoprotein-120 has been implicated in the development of neuropathic pain using evidence from in-vitro and in-vivo animal studies. Oh *et al.* [33**] explored more specific mechanisms using a rat dorsal root ganglion neuronal-culture model. They were able to show convincing evidence that many small nociceptive neurons express receptors for a highly diverse group of chemokines, that these can be activated by the respective chemokines and by glycoprotein-120, resulting in excitation and the release of substance P in a subgroup. Using a rat behavioral assay, they also showed the production of allodynia by intradermal injection of glycoprotein-120. This last aspect was explored in more detail in another study using the direct exposure of glycoprotein-120 to the rat sciatic nerve [34*]. The authors were able to show allodynia and hyperalgesia to various stimuli, local short-term nerve abnormalities and, perhaps more importantly, longer-lasting segmental spinal cord changes that correlated with the longer-lasting pain perception disturbances. Both of those

studies provided compelling evidence for the possible role of glycoprotein-120 in the development of neuropathic pain in HIV-1 infection.

Treatment

To date the only treatments for DSP that have proved effective in controlled trials are mainly symptomatic. A small placebo-controlled 14-week trial [35] showed that lamotrigine was effective in reducing pain in DSP, but the effect was not evident in dideoxynucleoside-associated polyneuropathy. An 18-week, randomized, placebo controlled trial of human recombinant NGF [31] showed a significant improvement in measures of neuropathic pain and pin sensitivity. More recently, results for the extended open-label use of NGF, a continuation of the aforementioned trial, have been published [36•]. Similar to what was reported in the double-blind phase, an improvement was observed in both dose groups of 0.1 and 0.3 $\mu\text{g}/\text{kg}$, with a greater improvement in those with higher average and maximum pain levels. There were no treatment differences between the arms, except when using combined-average pain levels in which high-dose NGF subgroups experienced lower pain levels and greater improvements. There were no changes in global pain measures from patient or investigator, and no significant changes in quantitative sensory testing or skin biopsy results. These results reiterate the effectivity of NGF in ameliorating painful DSP. However, despite the symptomatic effect of long-term NGF administration, they did not translate

into changes consistent with regeneration. The results of a small open-label study of gabapentin for the treatment of painful distal sensory neuropathy caused by HIV or neurotoxic therapies [37] suggested that this medication is also effective without significant interactions with antiretroviral treatment. The study provided further evidence for the effectiveness of gabapentin in this neuropathy, but was limited by the small size and the lack of a placebo-controlled arm (Table 1).

Conclusion

The fact that peripheral neuropathy is the most frequent and important neurological complication associated with HIV infection or its treatment is supported by studies in a variety of cohorts with different characteristics. Recent studies have provided important information about the mechanisms and methods of evaluation of this complication. Mitochondrial toxicity from dideoxynucleosides has now been demonstrated in nerves from affected patients, and could be modified by pre-existing mitochondrial defects. Further knowledge has been acquired about the association of neuropathy and markers of viral replication, and with measures of small fiber density. Questions have arisen about the significance of asymptomatic DSP and the risk of symptomatic DSP, as well as the balance between neurotoxicity and improved viral suppression. The effect of the aging of the HIV-infected population and the presence of coexistent infections will probably influence the frequency and spectrum of this complication and should be carefully investigated. Confirmed

Table 1. Summary of HIV neuropathies

Type of neuropathy	Stage of HIV infection	Electrophysiology	Proposed etiopathogenesis	Treatment
Acute and chronic inflammatory demyelinating neuropathy (Guillain-Barré syndrome, CIDP)	Early stages > Advanced stages	Segmental demyelination with slow conduction velocities, abnormal temporal dispersion and conduction block	Dysimmune Cytomegalovirus in late stages	Intravenous immunoglobulin Plasmapheresis; If HIV advanced (CD4 cell count < 100) and evidence of cytomegalovirus end-organ disease: consider ganciclovir, foscarnet or cidofovir
Distal sensory polyneuropathy	Middle and advanced stages	Diffuse distal sensory axonal loss with reduced-amplitude sensory action potentials	? Macrophage activation with increased pro-inflammatory mediators	Symptomatic: variety of pain-modifying agents
Mononeuropathy multiplex (opportunistic viral infections)	Advanced stages	Multifocal axonal and myelin damage with segmental slowing or axonal damage	Cytomegalovirus, varicella zoster	Ganciclovir, foscarnet, cidofovir, acyclovir, valacyclovir
Mononeuropathy multiplex (vasculitic)	Early stages	Multifocal sensory and motor axonal loss	Dysimmune or coexistent hepatitis B or C	Corticosteroids, IVIg, plasmapheresis
Polyradiculopathy	Advanced stages	Motor axonal loss, denervation with relative sparing of sensory nerve action potentials	Cytomegalovirus Rarely neurosyphilis, lymphoma	Ganciclovir, foscarnet, cidofovir
Diffuse infiltrative lymphocytosis syndrome	Advanced stages	Axonal loss, symmetric or multifocal, sensory or sensorimotor	Angiocentric infiltration of CD8 lymphocytes ? HIV-driven hyperimmune reaction	Not known
Antiretroviral toxic neuropathy	All stages	Symmetric sensory axonal loss with reduced-amplitude sensory action potentials	? Mitochondrial toxicity of dorsal root ganglion neurons	Variety of pain-modifying agents; discontinue 'd-drug'

CIDP, chronic inflammatory demyelinating radiculoneuropathy; IVIg, intravenous immunoglobulin. Modified from Keswani et al. [1•], with permission.

symptomatic therapies for DSP exist but are limited. There is a great need to expand the number of confirmed therapies and explore treatments that could potentially stop or reverse the damage.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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