

# Human Immunodeficiency Virus and the Peripheral Nervous System Workshop

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To provide a venue for a comprehensive multidisciplinary review of the current state of knowledge regarding the human immunodeficiency virus–associated peripheral neuropathies and to provide the institute with guidance in formulating future research initiatives, the National Institute of Neurological Disorders and Stroke (Bethesda, Md) convened a workshop on September 18 through 19, 2000. The participants were chosen from various disciplines and included clinicians, pathologists, neurobiologists, neurophysiologists, virologists, and neuroimmunologists. The present article summarizes the highlights of the meeting and includes the recommendations developed by the participants for future research. As might be expected in a rapidly evolving scientific field, the meeting was characterized by a lively and far-ranging discussion of data interpretation, experimental approaches, and priorities for future research. However, the recommendations presented at the end of this article constitute a consensus judgment reached by all of the participants of the most important areas for future research.

*Arch Neurol.* 2001;58:1561-1566

The workshop agenda [for a list of The Peripheral Nervous System Workshop committee and participants, see page 1565] included a review of the virology and immunology of the peripheral nervous system and pathogenic mechanisms involved in the development of peripheral neuropathies. Since participants came from diverse scientific disciplines, prior to the meeting, a series of position papers was prepared and circulated to provide a background basis for critical discussion of the agenda to pics. These position papers are published elsewhere.<sup>1-4</sup> Because pain is such a common symptom of human immunodeficiency virus type 1 (HIV-1)–associated peripheral neuropathy, a session was devoted to its consideration. A session was also devoted to the consideration of autonomic dysfunction in HIV-positive patients. The workshop concluded with a discussion of the toxicology

of antiretroviral drugs, their penetration into the peripheral nervous system, and the possibility of developing less toxic agents.

## MEETING SUMMARY

### Clinical Features of Acquired Immunodeficiency Syndrome Neuropathy

When acquired immunodeficiency syndrome (AIDS) was first recognized as a clinical entity, the attention of the medical community was focused on the systemic manifestations of the disease. As the number of cases increased, clinicians soon recognized that the brain was frequently affected by HIV-1 as well as a variety of opportunistic infectious agents. Shortly thereafter, scientists realized that involvement of the peripheral nervous system was also part of AIDS, and, like the brain, it was a target of both the virus and other infectious agents.

Although the development of neuropathic symptoms frequently does not occur until the patient exhibits the symptoms of

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early AIDS, electrophysiological evidence of peripheral nerve involvement is found in many patients with normal or near-normal CD4 cell counts. As one might expect, the incidence of peripheral neuropathy increases as the disease progresses, and it probably occurs to some extent in a majority of patients at the end stage of their disease. While pathological involvement of peripheral nerves is present virtually in all patients dying of AIDS, not all patients with HIV-1 infection develop clinical neuropathy. Peripheral neuropathic symptoms may remain unrecognized or unappreciated in the presence of additional lesions in the spinal cord or brain in end-stage AIDS.

The peripheral neuropathies associated with HIV-1 infection are a diverse group including acute and chronic inflammatory demyelinating polyneuropathy, mononeuropathy multiplex, and cytomegalovirus-(CMV) and herpes zoster virus-related neuropathies. The most common and clinically important neuropathy is distal sensory painful polyneuropathy (DSP).

Distal sensory painful polyneuropathy becomes symptomatic in the later stages of HIV infection as the CD4 cell count drops below a few hundred cells, although careful electrophysiological study may demonstrate subclinical DSP prior to the development of full-blown AIDS. It is not certain whether DSP results from elaboration of cytotoxic materials by virus-activated macrophages, other immune responses, or from productive virus replication within the peripheral nerves. It is clear that several members of the dideoxynucleoside family of nucleoside-analogue reverse-transcriptase inhibitors (NRTIs) used in highly active antiretroviral therapy (HAART) are significantly neurotoxic (stavudine, zalcidabine, didanosine). Therefore, although the incidence of pure HIV-1-associated DSP may have decreased in the last several years with the advent of effective HAART therapy, the incidence of drug-induced neurotoxicity has increased substantially.

The drug-induced component of the paresthesias associated with DSP is frequently so severe that it forces the patients to abandon a therapy that is otherwise optimal for their systemic or other neurological complications. The workshop concluded that it was vital to develop assessments to distinguish between drug-induced and HIV-1-associated DSP.

There are other comorbid processes that can complicate the management of DSP in HIV-1-infected patients, such as the diabetes or nutritional neuropathies. The other polyneuropathies, such as acute and chronic inflammatory demyelinating polyneuropathies and mononeuropathy multiplex, tend to occur earlier in the course of HIV-1 infection. In some patients, the inflammatory neuropathies are supplanted by DSP as the disease progresses. Cytomegalovirus-related polyradiculopathy occurs in patients with terminal AIDS, and its incidence seems to be declining with successful HAART.

### Pathology

Patients with HIV-1-associated neuropathies may have axonal, demyelinating, or mixed axonal and demyelinating

pathological features. While the virus is implicated in all these neuropathies, the predominantly demyelinating neuropathies are presumed to be immune mediated.

Distal sensory painful polyneuropathy, the most common HIV-1-associated neuropathy, is mainly axonal. It is termed a "dying-back" neuropathy because of its pattern of distal fiber loss. The major pathology consists of sensory axon involvement in a classical length-dependent fashion (ie, the more distal regions of a nerve fiber are the more severely affected). The loss of neurons in dorsal root ganglia (DRG) is less than the loss of axons in distal nerves. The loss of intradermal fibers is greater and is reported earlier than the dropout of fibers of adjacent sensory nerves.

Distal sensory painful polyneuropathy also involves sensory axons of all sizes, which distinguishes it from diabetic or uremic sensory neuropathy. The neuropathies that develop from the toxic effects of HAART therapy are very similar both to the pathological characteristics of DSP and to those of other toxic axonal neuropathies. They are a particularly common and important clinical problem.

The primary site of the pathology and the mechanism(s) that lead to DSP and toxic neuropathies are unclear. Changes in the gracile tracts as well as in the peripheral processes are involved in dying-back neuropathies, which suggests that the primary site and the chief insult could be at the level of the dorsal root ganglion (DRG). Such dying-back pathology could also theoretically occur secondary to extrinsic factors that would affect axons in a length-dependent fashion, such as in the presence of cytokines.

There is a paucity of virus and its infiltrates in the peripheral nerves of patients with HIV-1. It is widely accepted that almost all virus recovered from the peripheral nerve tissue is from the resident macrophage-monocytes that account for about 10% of the cells in the peripheral nerves. Axonal damage of any cause elicits some macrophage response at the site of the degenerating fiber in all neuropathies, but whether the macrophage response is greater or different in DSP is unknown.

It has been suggested that a local toxic microenvironment induced by activated macrophages could result in axonal damage and neuropathy in HIV-1 infection. It is known from bone marrow chimeras that blood and tissue macrophages turn over at a rapid rate. Some perivascular cells in peripheral nerves and the Langerhans cells in the vicinity of terminal axons in the skin are phenotypically related to the macrophage or monocyte lineage. Most satellite cells that surround the DRG neurons are also hematogenously derived and belong to the macrophage or monocyte family. Not only are these satellite cells in anatomic proximity with DRG neurons, but when the neurons receive any signal of peripheral insult, they respond. For example, satellite cell macrophages generally migrate to within close proximity of the cell body when the neuron is undergoing chromatolysis due to distal injury to the nerve fiber.

In patients with DSP, there is little evidence of intact virus, viral transcripts, or viral antigens in either the pe-

ripheral nerves or DRG. A similar paucity of virus presence can be detected in HIV-seropositive individuals without neuropathy, suggesting that virus recovery is from the normal resident macrophages and not from the extra recruited macrophages. A quantitatively similar viral load occurs in macrophages and microglial cells in both asymptomatic and cognitively impaired patients with HIV-1 infection. The unexpectedly consistent paucity of virus, despite the dramatic clinical and pathological changes in many patients argues that the virus may not be the direct or proximate cause of DSP. Nevertheless, the duration of infection and general increase in viral load are related to the occurrence of HIV-1 neuropathy. Consistent and prolonged suppression of viral copying and attendant suppression of viral numbers unequivocally result in a decline in the development of DSP. Whether DSP is the indirect effect of the systemic viral infection (conceivably produced by inflammatory cytokines and other toxic mediators) or whether the dying-back axonal neuropathy is the manifestation of sick DRG neurons is unclear.

Several NRTIs, usually didanosine, zalcidabine, stavudine, and possibly lamivudine produce axonal toxic neuropathy similar to DSP. Another related drug, fialuridine, which was used to treat patients with hepatitis, produced dose-dependent, irreversible axonal neuropathy. The other NRTI-induced toxic neuropathies tend to be reversible, although patients may show "coasting," meaning that they continue to worsen clinically and pathologically for a while, even after the discontinuation of treatment with the agents.

The risk factors for NRTI-induced neuropathies in patients with HIV-1 infection include the viral load, the cumulative dose of drug, the specific combination of NRTI, use of hydroxyurea, and the presence of another coexisting peripheral neuropathy. Sometimes clinicians can distinguish toxic neuropathy from DSP by the temporal relationship between the development of neuropathy and the use of NRTI, as well as by the stabilization and improvement of the neuropathy after discontinuation of the drug. However, it is frequently difficult or impossible to accurately assess the contribution by the toxic agent to the clinical symptomatology.

It is well known now that NRTIs produce toxicity by inhibiting the  $\gamma$  DNA polymerase that is needed for mitochondrial replication. The aceto-group in the structure of these agents competes for the thymidine group in mitochondrial DNA. The incorporation of an aceto-group in DNA terminates the chain because a new base cannot be added downstream.

In both acute and chronic inflammatory demyelinating polyneuropathies (IDP), teased nerve fibers show classical segmental demyelination and remyelination. The cellular infiltrates in IDP are scanty, mononuclear, and located predominantly in perivenular regions. It is usually not possible to isolate virus from the nerves of patients with acute IDP and chronic IDP, and in situ hybridization reveals no viral sequences. Patients with IDP and coexisting HIV-1 infection respond to immune modulating therapies in a manner similar to that of patients with IDP not associated with HIV-1 infection. However, the pathological changes in HIV-1-associated

IDP are somewhat different since the degree of pleocytosis in the cerebrospinal fluid, lymphocytic infiltrate in nerve tissue, and axonal loss is greater in patients with HIV.

The pathology in progressive polyradiculopathy is distinctive. There is CMV-mediated focal inflammation of the spinal nerve roots and adjacent spinal cord. Analysis of cerebrospinal fluid frequently shows polymorphonuclear pleocytosis in progressive polyradiculopathy. The presence of CMV can be demonstrated in various ways: by cytopathology, in situ hybridization, culture, or, more rapidly, by polymerase chain reaction. Early and aggressive anti-CMV treatment can result in arrest of the pathological process, followed by functional recovery. Although this neuropathy is somewhat unusual, an accurate and prompt diagnosis has positive therapeutic implications.

The rare neuropathy associated with diffuse infiltrative lymphomatosis is pathologically enigmatic. It is not a lymphoma. Some believe that it is pseudolymphoma involving multiclonal CD8 lymphocytes that, for some reason, have a predilection for peripheral nerves. In this respect, diffuse infiltrative lymphomatosis is akin to regional pseudolymphoma that involves the orbit.

### HIV-1 Neuropathy and Pain

Neuropathic pain in chronic diseases such as diabetic neuropathy, postherpetic neuralgia, and HIV-1-associated neuropathy is a major clinical problem. Unfortunately, existing animal models used to study neuropathic pain, such as ligature-induced peripheral nerve ischemia or dramatic nerve crush, probably do not involve the same mechanisms as in human neuropathic pain. They certainly lack the complexity of the human perception of pain. The workshop recognized the difficulty of the development of an animal model of neuropathic pain specifically featuring the mechanisms of HIV-1-associated neuropathy, and participants confirmed that such models are vital to understanding the causes of neuropathic pain.

Neuropathic pain can be differentiated into pain that is stimulus independent (ie, spontaneous pain, and stimulus-induced pain such as hyperalgesia). Hyperalgesia then, can be subdivided into pain produced by light mechanical stimulation such as allodynia, or pain resulting from either hot or cold thermal stimuli—a classification of some practical importance. In some instances, the intensity of the neuropathic pain perception depends on sensitization to a particular type of stimulus.

The hyperalgesia that often follows nerve injury is commonly explained by peripheral and central sensitization. In animal models, 2 types of hyperalgesia are recognized following cutaneous injury. Primary hyperalgesia occurs at the site of injury and probably results from sensitization of the peripheral nociceptive receptors. Secondary hyperalgesia occurs with sensitization of neurons in the central nervous system at the dorsal horn level and probably extending to higher-order neurons as well.

The sensitization of neurons in the central nervous system reflects their dynamic nature. In mature animals and under normal circumstances, these neurons receive continuous trophic support by retrograde axonal transport from their peripheral receptors. When primary sensory neurons lose contact with their peripheral receptors either from injury, loss of receptors, or damage to afferent nerve fibers, there is a concomitant loss of trophic support. Thus, one of the consequences of dying-back neuropathy, such as what occurs in distal sensory polyneuropathy associated with HIV, can be changes in the primary sensory neurons. There may be up- or down-regulation of their transmitter secretion, changes in the number of receptors, or changes in the character of their membrane ion channels. Furthermore, injured nerve fibers and presumably their cell bodies possess cytokine receptors and are capable of secreting a variety of proinflammatory and anti-inflammatory cytokines. In addition, macrophages are attracted to the injured area of a nerve. Upon their activation, they secrete additional cytokines and contribute to the complexity of the process of sensitization.

### Drug Treatment of Neuropathic Pain

Most of the currently available treatments for neuropathic pain have resulted from clinical trials in patients with diabetic neuropathy or postherpetic neuralgia. In most cases, the assessment of clinical efficacy has depended on meta-analysis of multiple trials. Generally, the effects have been modest, with perhaps a 25% to 30% reduction in the neuropathic pain of diabetic neuropathy or postherpetic neuralgia. The response in HIV-associated distal sensory neuropathy seems to be somewhat less. Three classes of drugs have been commonly used for the treatment of neuropathic pain: tricyclic antidepressants, anticonvulsants, and opioids. The mechanisms by which these drugs are thought to operate are diverse. Nonsteroidal anti-inflammatory agents and Cox-2 inhibitors probably work by blocking the response of peripheral receptors to prostaglandin-induced noxious stimuli at the periphery. Other agents probably act more centrally. The sodium channel blocker, mexiletine, probably works on the dorsal ganglion by blocking ectopic discharges in sensitized neurons. The tricyclic antidepressants, which increase the availability of norepinephrine and serotonin, may block nociceptive pathways at the secondary or tertiary neuronal level. Gabapentin and narcotic analgesics modify central pain transmission by their effects on  $\gamma$ -aminobutyric acid pathways and opioid receptors, respectively.

There are theoretical reasons for thinking that trophic factors might be effective in treating neuropathic pain, although a single trial of nerve growth factor showed no effect.

### The Role of HIV-1 and Other Viruses in the Pathogenesis of HIV-Associated Neuropathies

Type 1 HIV can be directly pathogenic by replicating in macrophages in peripheral nerve fibers or in the

supporting cells of peripheral nerve fibers. The virus does not seem to replicate in peripheral nerve fibers, although viral infection has been reported in dorsal root ganglion neurons. In the most common HIV-associated neuropathy, DSP, direct virus replication is probably of relatively minor importance; however, in the rare form of diffuse infiltrative lymphocytosis syndrome with neuropathy, large HIV-proviral loads can be detected. The importance of direct HIV replication is unclear in the other HIV-associated neuropathies such as progressive polyneuropathy, the inflammatory demyelinating polyneuropathies, and the mononeuropathy multiplex. However, it is probably of major importance in DSP. The role of cytomegalovirus infection was initially thought to be associated etiologically with the majority of HIV neuropathies. It has since been found to be only minimally and occasionally responsible for pathological changes, mostly in cases of polyneuroradiculopathy and mononeuropathy multiplex. In these neuropathies anticytomegalovirus therapy is beneficial.

Other viruses such as varicella zoster have been associated with peripheral nerve disease, mostly radiculopathy, in the end stages of AIDS.

### The Immunological Basis of Peripheral Neuropathies Associated With HIV Infection

Depending on the particular neuropathy, immunological factors and productive HIV viral replication vary in their contribution to the neuropathic etiology. In DSP, the amount of HIV virus detected and the extent of macrophage and lymphocytic infiltration vary considerably. No obvious immunopathogenic mechanism has been identified as the proximate cause of DSP (neuropathy) although activated macrophages are known to produce a wide variety of cytokines in both the peripheral nerves and dorsal root ganglia. It is possible that the monocytes found in abundance in the dorsal root ganglia might subsume functions similar to the microglial cells of the central nervous system. It is also possible that the neuronal and axonal damage results from loss of trophic agents no longer secreted by activated macrophages rather than the toxic effects produced by secreted cytokines.

Different immunological mechanisms are probably involved in the cause of the other HIV-associated peripheral neuropathies. A reasonable but unproven assumption is that the inflammatory demyelinating polyneuropathies result from an immunological attack similar to that found in the classical Guillain-Barré-like disorders that they resemble clinically.

The mononeuritis multiplex neuropathy seems to be basically a necrotizing vasculitis with features similar to those found in polyarteritis nodosa and other hypersensitivity angiitides.

In the rare forms of diffuse infiltrative lymphocytosis polyneuropathy, there is a marked CD8 lymphocytic infiltration that may represent an abnormal lymphocytic response to HIV virus in the nerve itself.

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The different infectivity of different virus strains may be due to the well-known ability of the HIV-1 virus

to develop polymorphisms that allow more than 1 genetic variant to be present in a single individual. Viruses that infect macrophages commonly use the receptor CCR5 to attach to the cell surface. T-cell lines lack the CCR5 receptor, and viral strains that infect them use the CXCR4 receptor. Other virus strains can use either the CCR5 or the CXCR4 receptor, and these viruses can infect both macrophages and T-cell lines. In a well-recognized human genetic polymorphism, the CCR5  $\Delta$  32 mutation, a base pair deletion at position 32 creates a frame shift deletion that then results in a nonfunctional CCR5 receptor. Therefore, the macrophages in individuals who are homozygous for the CCR5  $\Delta$  32 mutation are essentially immune from invasion by many of the HIV-1 viral strains. This lower infectivity in individuals with the CCR5  $\Delta$  mutation may explain why these patients have a more benign course of infection and have a smaller viral load.

## RECOMMENDATIONS

### Painful Neuropathy

A major conclusion of the workshop was that both HIV infection per se and the neurotoxicity of certain drugs in HAART contribute to the development of painful peripheral sensory neuropathy. The cause of the HIV-associated neuropathy merits extensive investigation to determine the relative roles of the viral infection and the activation of immunological factors that contribute to the pathogenesis of the damage in axons, dorsal root ganglia, and the sensory tracks in the spinal cord.

In addition, the mechanism(s) by which HAART drugs produce toxic side effects should be studied with the goal of developing drugs that are not toxic, or developing ancillary agents that could block the toxic effects of the HAART drugs without reducing the therapeutic effects.

### Pain

The pain associated with sensory neuropathy needs to be investigated from several aspects. There are probably common mechanisms by which diverse types of axonal and dorsal root damage result in pain in neurological diseases. For this reason, research to determine the main factors that contribute to the onset of pain in HIV-associated sensory neuropathy will be of general benefit to clinicians dealing with pain.

There is a need for both physiological and pathological tools to identify precisely the lesion(s) that cause pain. In particular, the role of the dorsal root ganglia and ascending spinal cord tracks in the production of neuropathic pain merit study. Skin biopsy specimens may prove to be a useful tool in correlating pathological changes in the distal nociceptive fibers with pain perception.

From a clinical point of view, it would be useful to identify and quantify more precisely the types of pain associated with HIV-associated peripheral neuropathy. Clinical tools also need to be developed to quantify the magnitude of discomfort produced by pain. These tools

may be useful for assessment of potential strategies to control pain.

### Neuroimmunology

Immunopathological processes seem to play important roles in the development of peripheral nervous system injury, so there is a need for basic neuroimmunological studies. In particular, research is needed to determine the factors that govern macrophage activation and recruitment in the peripheral nervous system, as well as to understand the ability of these cells to modulate immunopathological reactions in the peripheral nerve, dorsal root ganglia, and the dorsal horn of the spinal cord. The role of cytokines and chemokines as modulators of inflammatory reactions and injury is of particular interest.

### Animal Models

The workshop participants recognized that the availability of animal models is essential for the experimental study of sensory neuropathy. Despite the difficulties of primate research, some questions are best addressed by the simian immunodeficiency virus monkey model.

Research using this animal model should be encouraged. A wider availability of the WLD mouse would be helpful in assessing basic issues related to mechanisms of nerve and axonal degeneration. The use of in vitro models such as dorsal root ganglia and organotypic spinal cord cultures to investigate the effect of viral proteins or antiretroviral agents on nervous tissue is also recommended.

Accepted for publication July 23, 2001.

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