HIV neuropathy: Insights in the pathology of HIV peripheral nerve disease

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Abstract  HIV-associated neuropathies (HIV-N) have become the most frequent neurological disorder associated with HIV infection. The most common forms of HIV-N are the distal sensory polyneuropathy (DSP) and antiretroviral toxic neuropathies (ATN), disorders characterized mostly by sensory symptoms that include spontaneous or evoked pain that follow a subacute or chronic course. The main pathological features that characterize DSP and ATN include “dying back” axonal degeneration of long axons in distal regions, loss of unmyelinated fibers, and variable degree of macrophage infiltration in peripheral nerves and dorsal root ganglia. Marked activation of macrophages as well as the effect of pro-inflammatory cytokines appear to be the main immunopathogenic factors in DSP. Interference with DNA synthesis and mitochondrial abnormalities produced by nucleoside antiretrovirals have been hypothesized as pathogenic factors involved in ATN. The use of skin biopsy has become a useful tool in the evaluation of HIV-N. Reduction in fiber density, increased frequency of fiber varicosities and fiber fragmentation are prominent features of skin biopsies from patients with HIV-N. Other forms of HIV-N include acute or chronic inflammatory polyneuropathies, uncommon disorders that may occur during seroconversion or early stages of HIV infection. Opportunistic infections, mostly associated with cytomegalovirus or herpes zoster virus infection occur in late stages of AIDS and produce characteristic clinical features such as mononeuritis multiple or radiculopathies.

Key words: HIV neuropathy, polyneuropathy, macrophage, dorsal root ganglia, skin biopsy

Introduction

The involvement of the peripheral nervous system in HIV infection has been one of the most challenging aspects of the AIDS epidemic. With the effectiveness of antiretroviral treatment and the consequent decline in the incidence rates of CNS opportunistic infections and HIV dementia, HIV-associated neuropathies have become the most common neurological disorders associated with AIDS. Either as the result of the direct effect of immunological dysregulation produced by HIV infection, opportunistic infections, or neurotoxic antiretrovirals, involvement of the PNS may occur at different stages of the disease with distinctive clinical, electrophysiological and neuropathological features (Araujo et al., 2000; Comblath and McArthur, 1998; Dalakas and Cupler, 1996; Dalakas and Pezeshkpour, 1988; Fuller et al., 1993; Price, 1996; Wulff et al., 2000).

Clinical-pathological issues

The HIV-associated neuropathies can be classified on the basis of when they occur with respect to the HIV disease stage, and by clinical course and major symptoms (Budka et al., 1991). Some types of peripheral neuropathies appear to be more frequent during particular stages of HIV, presenting characteristic clinical features, progression, immunopathogenic mechanisms and response to treatment (Griffin et al., 1998; Wulff et al., 2000) (Table 1). The most common HIV-associated neuropathy is the distal sensory polyneuropathy (DSP), a disorder characterized mostly by sensory
symptoms, often including spontaneous or evoked pains with a subacute and chronic course, usually developing during the advanced stages of AIDS (Cornblath and McArthur, 1988; Fuller et al., 1993; Hall et al., 1991; Leger et al., 1989). Clinical and electrophysiological studies suggest that DSP is predominantly an axonal neuropathy. In some patients, DSP may coexist with a toxic neuropathy associated with the use of specific nucleoside antiretrovirals. Frequently, such toxic neuropathies are difficult to differentiate from DSP because they share similar clinical features (Fichtenbaum et al., 1995; Moyle, 2000; Moyle and Sadler, 1998; Simpson and Tagliati, 1995). The dideoxynucleoside analogues ddC, ddI and d4T have been linked to mitochondrial toxicity through selective inhibition of γDNA polymerase (Lewis and Dalakas, 1995). Occasionally the toxicity manifests itself as lactic acidosis or acute sensory neuropathy. Inflammatory demyelinating polyneuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP) and acute inflammatory demyelinating polyneuropathy (AIDP) are less common but can occur in the setting of HIV infection, often during seroconversion, before AIDS or immunosuppression (Cornblath et al., 1987; Dalakas and Cuper, 1996; Dalakas and Pesezhkpor, 1988; de la Monte et al., 1988; Lipkin et al., 1987; Piette et al., 1986; Thornton et al., 1991). The most important electrophysiological feature is the presence of a demyelinating neuropathic process, but frequently an axonal component is observed. The clinical course is either acute (AIDP), or subacute and chronic (CIDP), with both motor and sensory symptoms. Op-

Table 1. PNS involvement in HIV infection

<table>
<thead>
<tr>
<th>HIV-associated PNS disorder</th>
<th>CDC stage</th>
<th>Course</th>
<th>Clinical features</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Distal Sensory Neuropathy</td>
<td>Sensory neuropathy</td>
<td>AIDS, CDC C</td>
<td>Subacute or chronic</td>
<td>Distal, sensory loss, neuropathic pain</td>
</tr>
<tr>
<td>II. Toxic antiretroviral-associated neuropathies</td>
<td>Antiretroviral toxic neuropathy</td>
<td>Any stage, CDC A-C</td>
<td>Subacute or rarely acute with lactic acidosis</td>
<td>Sensory, motor, neuropathic pain</td>
</tr>
<tr>
<td>III. Mononeuritis multiple</td>
<td>Vasculitic mononeuritis multiple</td>
<td>Symptomatic HIV disease, CDC B</td>
<td>Stepwise progression</td>
<td>Multiple mononeuritis, sensory</td>
</tr>
<tr>
<td>CMV multiple mononeuropathy</td>
<td>AIDS, CDC C</td>
<td>Acute, subacute</td>
<td>Multiple mononeuritis</td>
<td></td>
</tr>
<tr>
<td>IV. Inflammatory Demyelinating Polyneuropathies</td>
<td>Guillain-Barré syndrome (GBS) or Acute inflammatory demyelinating neuropathy [AIDP]; -demyelinating form -acute motor-sensory axonal neuropathy</td>
<td>Early, pre-AIDS, AIDS</td>
<td>Acute</td>
<td>Weakness</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating neuropathy [CIDP]</td>
<td>Early, pre-AIDS, AIDS</td>
<td>Progressive</td>
<td>Weakness</td>
<td></td>
</tr>
<tr>
<td>V. Opportunistic infection-associated neuropathies</td>
<td>CMV polyradiculopathy</td>
<td>AIDS</td>
<td>Acute</td>
<td>Pain, cauda equina</td>
</tr>
<tr>
<td>Herpes zoster radiculopathy or myeloradiculopathy</td>
<td>AIDS</td>
<td>Acute</td>
<td>Pain, motor dysfunction</td>
<td></td>
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<tr>
<td>VI. Other</td>
<td>Sensory neuropathy/dorsal radiculopathy</td>
<td>Early, pre-AIDS, AIDS</td>
<td>Subacute or chronic progression</td>
<td>Sensory, gait ataxia</td>
</tr>
<tr>
<td>Diffuse infiltrative lymphocytosis syndrome</td>
<td>AIDS</td>
<td>Subacute</td>
<td>Symmetric or asymmetric sensorimotor, painful, multiple mononeuritis, distal sensory neuropathy</td>
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<tr>
<td>CD8 hyperlymphocytosis, vascular mural necrosis</td>
<td>AIDS</td>
<td>Subacute</td>
<td>Symmetric or asymmetric sensorimotor, painful, multiple mononeuritis, distal sensory neuropathy</td>
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</table>
portunistic infections such as CMV and VZV may involve the PNS, mostly in the intermediate and late stages of AIDS. Progressive polyradiculopathies are frequently associated with CMV infection, mostly in the very late stages of AIDS when the CD₄ count is below 50 cells/mm² (Anders and Goebel, 1999; Baudrimont and Moullignier, 1997; Corral et al., 1997; Grafe and Wiley, 1989; Kim and Hollander, 1993; Lipkin et al., 1987; Said et al., 1991). VZV infection of the PNS manifests itself mostly as a sensory ganglionitis and myeloradiculitis often characterized by sensory symptoms and pain (Brown et al., 1988; Henin et al., 1995; Lipkin et al., 1987; Oh et al., 1999). Mononeuritis multiplex (MM) may also present in the early stages of AIDS as a manifestation of a vasculitic neuropathy (sometimes associated with hepatitis B or C) (Cacoub et al., 2000) or during the late stages as the result of CMV infection (Dalakas and Cupler, 1996). Finally, nutritional-related (vitamin B₁₂, alcohol) and entrapment neuropathies can also occur in the setting of HIV infection (Griffin et al., 1998).

Neuropathology of HIV-associated neuropathies

The neuropathological analysis of HIV-associated neuropathies should focus on the different central and peripheral nervous system structures associated with sensory pathways, including spinal cord, dorsal root ganglia (DRG), peripheral nerve and cutaneous nerve fibers. The majority of pathological studies available on HIV-associated neuropathy have focused on the evaluation of the peripheral nerve, often from sural nerve biopsies, and the DRG. Few studies have examined the pathology of sensory pathways in the spinal cord or skin nerve fibers.

Peripheral nerve pathology
Distal sensory polyneuropathy

This form of HIV-associated neuropathy occurs clinically in the intermediate and late stages of AIDS, although subclinical and neuropathological evidence may be noted early. The most characteristic pathological feature is the axonal degeneration of long axons in distal regions (Cornblath and McArthur, 1988; de la Monte et al., 1988; Fuller et al., 1993; Griffin et al., 1998; McCarthy et al., 1995). The axonal damage follows the “dying back” pattern of degeneration. In DSP, the density of both small myelinated fibers and large myelinated fibers is reduced, but particularly the density of unmyelinated fibers is reduced (Fig. 1A) (Araujo et al., 2000). One morphometric study demonstrated an average reduction of 27% in myelinated fibers in DSP as compared with controls (Griffin et al., 1998). The magnitude of fiber reduction resembles the profile of other neuropathies such as amyloidosis and diabetic neuropathy that have a predominant small sensory fiber reduc-

![Figure 1. A) Focal loss of unmyelinated fibers in a sural nerve biopsy from a patient with DSP (toluidine blue). B) and C) Macrophages infiltration of peripheral nerve as observed by immunocytochemistry with anti-CD68 antibodies (B: cross section; C: longitudinal section) (bar 50 μm).](image)

tion. Immunopathological studies have shown prominent macrophage activation (Figs. 1B, 1C) with release of proinflammatory cytokines in areas of axonal degeneration. In some cases there is also subtle to prominent infiltration by lymphocytes of the epineurium (Chaunu et al., 1989; Dalakas and Pezeshkpour, 1988; de la Monte et al., 1988; Griffin et al., 1998; Mah et al., 1988; Robert et al., 1989).

Antiretroviral toxic neuropathies (ATN)

ATN can be indistinguishable from DSP except that the exposure to nucleoside antiretroviral medication appears to be an obvious risk factor (Fichtenbaum et al., 1995; Moyle, 2000; Moyle and Sadler, 1998; Simpson and Tagliati, 1995). Neuropathological studies suggest that both DSP and ATN share similar features, which include axonal degeneration and prominent loss of unmyelinated fibers (Dalakas and Cupler, 1996; Simpson and Tagliati, 1995). However, the reality is that detailed neuropathological analysis has not been completed. Prominent mitochondrial disruption and cristae abnormalities have been described with the use of some nucleoside antiretrovirals and it has also been linked to interference with mitochondrial DNA synthesis (Chen et al., 1991; Lewis and Dalakas, 1995; Moyle, 2000). Myelin changes including myelin splitting and edema have been observed in animal models of ddl peripheral neurotoxicity (Patterson et al., 2000).

Inflammatory demyelinating polyneuropathies

Although uncommon relative to DSP, both CIDP and AIDP typically occur during early HIV infection (Cornblath et al., 1987; de la Monte et al., 1988; Griffin et al., 1998; Piette et al., 1986; Said et al., 1988; Thornton et al., 1991). The peripheral nerve pathology observed in sural nerve biopsies of HIV-associated CIDP is similar to the cases of non-HIV-infected patients (Griffin et al., 1990; Griffin et al., 1995). In the early phases of CIDP, pathological changes are characterized by lym-
phocytic and macrophage infiltration and demyelination (Cornblath et al., 1987; de la Monte et al., 1988; Leger et al., 1989). At later stages, profiles of remyelination, presence of onion bulbs, paucity of lymphocytic infiltration, and a reduction in the density of small myelinated and unmyelinated fibers are the predominant features (Griffin et al., 1998). In contrast, the pathological profile of HIV-associated AIDP appears to be more complex and heterogeneous, similar to Guillain-Barré syndrome (GBS) forms in non-HIV infected patients (Griffin et al., 1995). Two clinicopathological variants of GBS (or AIDP) may be identified, a demyelinating form that appears to be more frequent and the axonal form. In the HIV-associated AIDP demyelinating form, an immune attack on the Schwann cell or myelin structure occurs and appears to be mediated by macrophages. In such cases and contrary to the non-HIV forms of GBS, the inflammatory infiltration of the peripheral nerve and roots is comprised mostly by CD8 lymphocytes. In addition, macrophage infiltration and activation is prominent as noted by immunocytochemical analysis (Cornblath et al., 1987; Griffin et al., 1998). Few cases of the axonal form of HIV-associated AIDP have been evaluated pathologically. At Johns Hopkins Hospital, the biopsy of one such patient showed mostly Wallerian degeneration changes, minimal evidence of inflammation and no demyelination (Griffin et al., 1998). Other studies of GBS cases have also found prominent axonal component in neuropathological studies (de la Monte et al., 1988; Said et al., 1988). In few cases of AIDP, CMV inclusions in Schwann cells have also been found (Dalakas and Pezeshkpour, 1988; Eidelberg et al., 1986; Mezin et al., 1991).

Mononeuritis multiplex

MM has been described in patients with HIV infection or early stages of AIDS. This form appears to be predominantly vasculitic as the pathological studies of the sural nerve disclosed evidence of necrotizing vasculitis. The potential role of immune complex attack associated with hepatitis B and C or cryoglobulins as the main immunopathological mechanism has been proposed (Dalakas and Pezeshkpour, 1988; Libman et al., 1995; Vernant et al., 1994; Younger et al., 1996). CMV infection is also involved in the presence of a form of multiple mononeuropathy in late stages of AIDS. This CMV-associated MM is characterized pathologically by CMV inclusions in endothelial cells, focal demyelination and Wallerian degeneration (Robert et al., 1989; Roulet et al., 1994; Said et al., 1991).

Opportunistic infections

Progressive polyradiculopathies associated with CMV infection are common in late stages of AIDS. The extension of the CMV cytopathic effects may involve endothelial cells and Schwann cells in the nerve and roots as well as DRG and spinal cord. Some pathological analyses have shown demyelinating and necrotizing features (Anders and Goebel, 1999; Baudrimont and Mouldgner, 1997; Corral et al., 1997; Grafe and Wiley, 1989; Kim and Hollander, 1993; Lipkin et al., 1987; Robert et al., 1989; Roulet et al., 1994; Said et al., 1991).

Diffuse infiltrative lymphocytosis syndrome (DILS)

DILS is a rare condition in which a persistent CD8 lymphocytosis can produce involvement of several organs, including the PNS. This rare form of sensorimotor neuropathy is characterized by the angiocentric infiltration by CD8 cells and vascular mural necrosis. Increased expression of HIV p24 has been demonstrated in macrophages infiltrating the nerves (Berger and Simpson, 1998; Gherardi et al., 1998; Moulignier et al., 1997; Price, 1998).

DRG pathology

Previous neuropathological studies in populations of HIV patients have shown variable degrees of involvement of the DRG with changes associated mostly with inflammation (Nagano et al., 1996b; Rizzuto et al., 1995; Scaravilli et al., 1992; Shapshak et al., 1995; Yoshioka et al., 1994). The most important features of the neuropathology in the DRG of patients with HIV neuropathy appear to be the presence of inflammatory cells, comprised mostly of lymphocytes and activated macrophages/microglia cells (Figs. 2A, 2C). In many of these patients, a decreased number of DRG neurons and increased frequency of Nageotte nodules have been demonstrated (Bradley et al., 1998; Nagano et al., 1996a; Rizzuto et al., 1995). The presence of infection by HIV of DRG neurons is still controversial. HIV infection of DRG neurons detected by PCR in situ hybridization has been shown in both groups of patients with HIV neuropathy and HIV seropositive controls without neuropathy (Brannagan et al., 1997). Other studies have identified the presence of the virus predominantly in perivascular inflammatory cells and in the nodules of Nageotte (Nagano et al., 1996a; Yoshioka et al., 1994). However, the most consistent pathology in the DRG appears to be the activation of inflammatory mechanisms that leads to injury of DRG neurons and the subsequent loss of inputs to central sensory pathways. Presence of proinflammatory cytokines such as TNF-α, IFN-γ and IL6, as well as other mediators of inflammation such as nitric oxide, has been consistently demonstrated in the DRG of patients with HIV infection (Nagano et al., 1996a; Yoshioka et al., 1994).

Spinal cord pathology

Few studies have focused on the pathological changes in the spinal cord associated with HIV neurop-
athy. Selective degeneration of gracile tract in patients with sensory neuropathy, characterized by loss of axons and myelin sheaths in the cervical and upper thoracic cord, described and suggested a “dying-back” degeneration process of DRG neurons (Dal Pan et al., 1994; Rance et al., 1988; Scaravilli et al., 1992). Other studies have shown a frequent presence of peripheral neuropathy in patients with vacuolar myelopathy (Brew, 1994; Dal Pan et al., 1994; Grafe and Wiley, 1989; Tan and Guiloff, 1998).

Epidermal nerve fiber pathology

The recent introduction of epidermal nerve fiber analysis by immunocytochemical techniques using the panaxonal marker PGP 9.5 (protein gene product 9.5), a neuronal ubiquitin hydrolase, has contributed to the investigation of PNS disorders. This technique allows the study of epidermal innervation by small-caliber C and Aδ nerve fibers (Holland et al., 1997; McCarthy et al., 1995). Studies of skin biopsies of patients with HIV-associated sensory neuropathy developing during treatment with didanosine or zalcitabine showed reduction in the number of epidermal fibers in distal areas of the lower extremities with an inverse correlation between neuropathic pain intensity and epidermal nerve fiber density (Polydefkis M, 2000). In some of these patients, there was an increase in the frequency of fiber varicosities and fragmentation in the dermis likely to be representative of degenerating fibers and absence of PGP 9.5 fibers in the epidermis (Fig. 3). There were also fewer epidermal fibers in HIV-seropositive patients without clinical evidence of neuropathy than in seronegative controls. This finding suggests that HIV infection may be associated with the loss of cutaneous innervation even before the onset of sensory symptomatology (McCarthy et al., 1995). A recent clinical trial that evaluated the use of nerve growth factor in the treatment of HIV-associated sensory neuropathy used epidermal nerve fiber density analysis as a secondary therapeutic outcome (McArthur et al., 2000).
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References


