Peripheral Neuropathies in HIV-infected Patients in the Era of HAART

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Introduction

Before the introduction of highly active antiretroviral therapy (HAART), neuromuscular disorders were found in approximately 10 to 20% of patients with HIV-infection, and sub-clinical evidence of peripheral neuropathy could be detected in 50 to 90% of patients with AIDS (15). HIV-associated peripheral neuropathies classically include inflammatory demyelinating polyneuropathy (IDP), focal peripheral nervous system involvement manifesting by mononeuropathy simplex or multiplex (MM) or polyradiculopathy, and distal sensory polyneuropathy (DSP), a length-dependent axonopathy (26, 39). The occurrence of the different types of neuropathy is related to the stage of illness and the degree of immunodeficiency. Acute or chronic IDPs tend to occur at the initial stages of the infection and become rarer as immune function deteriorates (26). Focal neuropathies develop in patients with or without AIDS and may result from various types of vasculitis (18) or Cytomegalovirus (CMV) infection (36). DSPs constitute by far the most common neuropathy in HIV-infected patients (37). They tend to occur in full blown AIDS and worsen as the number of CD4 cells decreases within blood (3, 9, 27, 37).

Introduction of HAART had a significant impact on the epidemiology of HIV-1-associated neuropathies (42). It was shown that the prevalence of the 2 most common HIV-associated disorders, HIV-associated dementia and DSP significantly decreased after introduction of HAART (31). Moreover, occurrence of both conditions was observed at a higher range of CD4 cell count in recent years (31). Likewise, both toxoplasma encephalitis and CMV-neuropathy appear to be on the decline (31, 42). On the other hand, there has been an increase in the prevalence of toxic neuropathies which seems mainly related to anti-retroviral nucleoside analogues. Interestingly, neurotoxic complications may be more likely to occur as the survival of HIV-infected individuals becomes longer due to more effective HIV-1 suppression and control of opportunistic infections.

This review of the impact of highly active antiretroviral therapy on peripheral neuropathies in HIV-1 infected individuals will consider on the one hand, peripheral nerve involvement related to HIV-1 infection and, on the other hand, peripheral nerve involvement secondary to the neurotoxicity of antiretroviral drugs.

The Role of HIV-1 in Peripheral Nervous System Involvement in HIV-infected Patients

It is currently believed that there is a link between several types of HIV-associated neuropathies and retroviral load. This view has been substantiated in the particular setting of diffuse infiltrative lymphocytosis syndrome (DILS) and may also apply to DSP and HIV-associated ALS-like syndromes.

Diffuse infiltrative lymphocytosis syndrome (DILS). The number of CD8 T-cells is often moderately and transiently elevated in the course of viral infections, including in the early stages of HIV infection (45). A subset of HIV-infected patients (4.3% in France) develop a condition known as persistent CD8 hyperlymphocytosis (10). A subgroup of patients with CD8 hyperlymphocytosis develop a syndrome that mimicks Sjogren's syndrome and is associated with multivisceral CD8 T-cell infiltration, known as the diffuse infiltrative lymphocytosis syndrome (DILS) (21). Patients with DILS tend to have higher CD4 cell counts, fewer opportunistic infections, and longer survival times than other HIV-infected patients. DILS is associated with predominant HLA-DR5 and HLA-DR6 phenotypes and likely reflects a particularly strong host response to HIV infection (22).

PNS may be involved in the course of DILS. In a series of 12 patients with DILS-associated peripheral neuropathy (33), the neuropathy was either acute or subacute, always painful, and most often symmetrical (in 8 of 12 patients). Electrophysiology was consistent with axonal neuropathy in 10 of 12 patients. Nerve biopsy showed marked angiocentric CD8 infiltrates without mural necrosis and abundant expression of HIV p24

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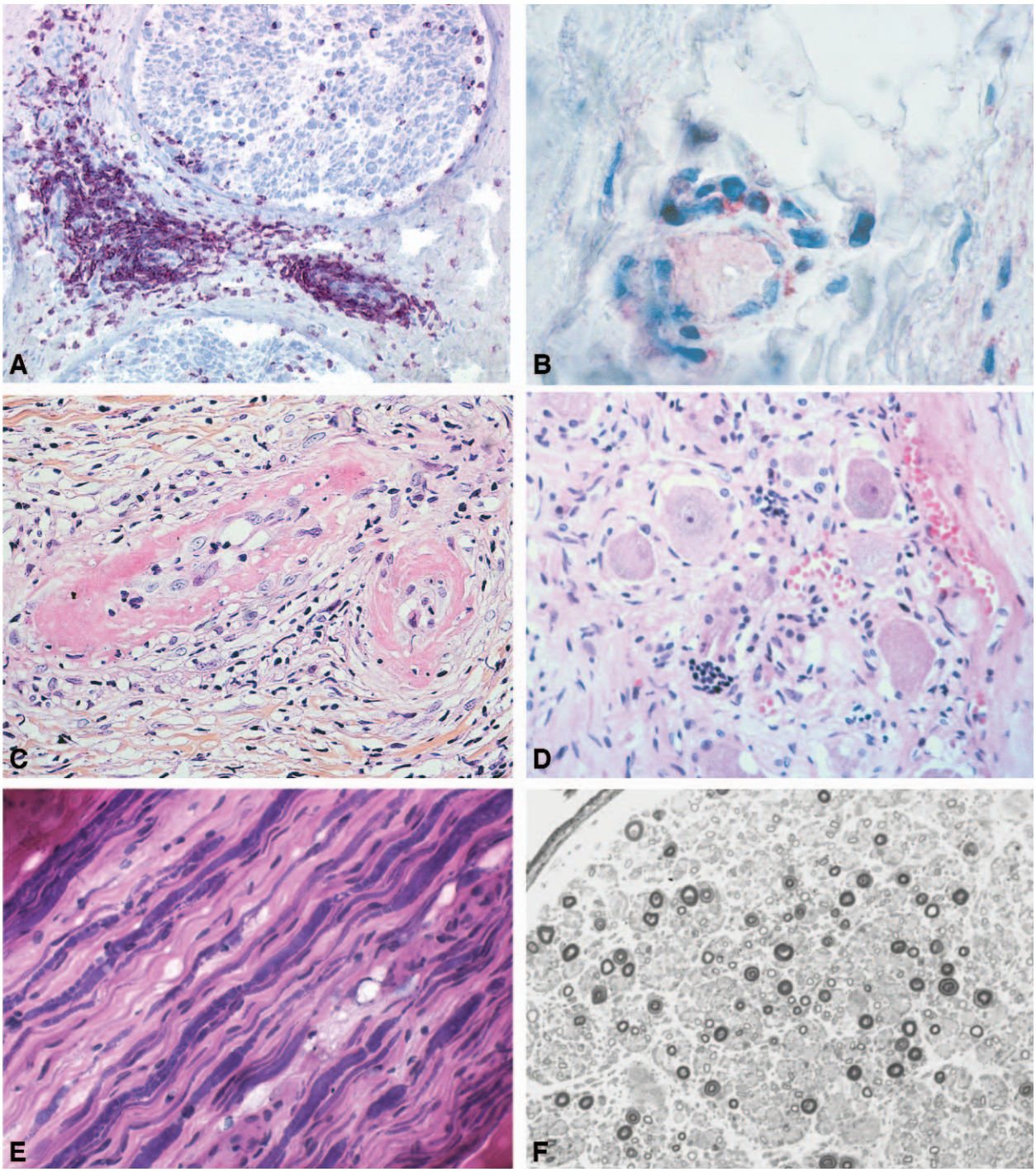

Figure 1. Nerve biopsy findings in patients with HIV-associated neuropathies. Diffuse infiltrative lymphocytosis syndrome: (**A**) Marked angiocentric CD8 T-cell infiltration in both epineurium and endoneurium (frozen section, immunohistochemistry, APAAP, ×100); (**B**) Perivascular cells, presumably macrophages, showing p24 immunoreactivities (frozen section, immunohistochemistry, APAAP, ×400). HIV-infected patients with persistent CD8 hyperlymphocytosis: (**C**) Fibrinoid necrosis in epineural vessel wall nerve (paraffin section, hematein-eosin-safran, ×100). Distal sensory polyneuropathy and dorsal root ganglia involvement: (**D**) Neuronal loss and residual nodules of Nageotte in a dorsal root ganglion from a HIV-1 infected patient with DSL (paraffin section, H&E, ×100). NRTI-induced (toxic) distal sensory polyneuropathy: (**E, F**) Axonopathy assessed by myelinated fiber loss (**E, F**), Wallerian degeneration (**E**) and clusters of regenerating fibers (**F**) (**E**: frozen section, hematein-eosin, ×400; F: semithin section, toluidin blue, ×400).

protein in macrophages that was detected in all twelve patients (Figure 1A-B) (33). In some patients DILS could be mistaken for a malignant lymphomatous process on the basis of nerve biopsy findings. Indeed, T-lymphocyte proliferative disorders may present as a spectrum of angiocentric immunoproliferative lesions (AIL), ranging from benign-appearing lymphocytic vasculitis (AIL1) to lymphomatoid granulomatosis (AIL2) and angiocentric lymphoma (AIL3) (23). To determine whether CD8 lymphoid infiltrates in nerves of patients with DILS correspond to a lymphomatous neoplastic process or to a proliferation of T-cells in response to HIV infection, we looked for the presence of monoclonal T-cells and evaluated HIV-1 proviral load, using PCR-based techniques, in frozen peripheral nerve samples from 6 patients with DILS neuropathy and 22 patients with other HIV-associated peripheral neuropathies, including mononeuritis multiplex (MM:6), inflammatory demyelinating polyneuropathies (IDP:6), distal sensory polyneuropathy (DSP:5), and toxic distal sensory polyneuropathy (TDSP:5). Five of 6 patients with DILS showed no detectable monoclonal T-cell clone in their nerves whereas a massive HIV-1 proviral load was found in 6 of 6 nerve samples. Nerve proviral load was 10^5-fold higher in DILS than in any of the other types of HIV-associated neuropathy (Figure 2) (20). These results indicate that DILS is a distinct entity among HIV-associated neuropathies, characterized by massive HIV proviral load in nerve, that must not be mistaken for a peripheral nerve T-cell lymphoma. Interestingly, in the initial series of 12 patients with DILS-associated neuropathy, zidovudine therapy was associated with improvement in 6 of 6 treated patients and steroid therapy was beneficial in 4 of 5 (33). Taken together, these results provide the best evidence for a possible direct association between HIV replication and HIV-associated peripheral neuropathy (25).

Interestingly, a subset of patients with necrotizing arteritis affecting the PNS may also show active local replication of HIV as assessed by in situ hydridization of HIV genome (19) and ultrastructural detection of HIV-like particles in perivascular macrophages (18). We had the opportunity to detect such cases with necrotizing arteritis of the nerve among HIV-infected patients presenting with persistent CD8 hyperlymphocytosis (Authier and Gherardi, unpublished data) (Figure 1C).

Distal sensory polyneuropathy (DSP) and dorsal root ganglia (DRG) involvement. It has been repeatedly proposed that HIV replication within the dorsal root ganglia (DRG) and peripheral nerve may contribute to the development of DSP. Neuronal loss and residual nodules of Nageotte may be seen in dorsal root ganglia from patients with DSL (Figure 1D). Several authors have detected HIV RNA by in situ hybridisation, and HIV protein p24 and/or gp41 by immunohistochemistry, in a proportion of peripheral nerve biopsy samples (Rizzuto et al, 1995: 6/13) (35) and DRG (Esiri et al, 1993: 7/12; Yoshioka et al, 1994: 5/16; Rizzuto et al, 1995: 2/15; Shapshak et al, 1995: 4/15) (16, 43, 35, 38) of patients known to have HIV infection (16), or AIDS (38, 43) or documented DSP (35). Thus, an approximate proportion of 50% of DSP cases may show HIV-1 within rare PNS macrophages. A more consistent feature is the presence of abundant activated macrophages that are nearly always observed. These macrophages markedly express MHC class I and II antigens and pro-inflammatory cytokines such as TNFα, IL-1 and IL-6 (15, 16, 35, 40, 44). Interestingly, DNA fragmentation assessed by in situ end-labelling (ISEL) was detected in the DRG neurons of 9 of 19 patients with AIDS, ISEL-positive neurons being more abundant in patients with axonal peripheral neuropathy (1). It seems likely that storage of HIV-1 in macrophages may both constitute a reservoir for the virus and act as a putative cause of PNS damage, probably through release of neurotoxic molecules and/or interaction with trophic factors (41). Therefore, it is possible that in addition to its preventive effect on the development of DSP, HAART could improve the neu-

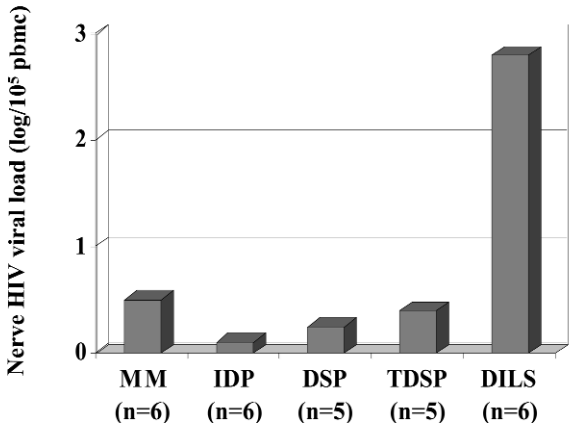

Figure 2. HIV-1 proviral load evaluated by semi-quantitative nested PCR in nerve samples from patients with diffuse infiltrative lymphocytosis syndrome (DILS) and other HIV-associated neuropathies (MM: mononeuropathy multiplex; IDP: inflammatory demyelinating polyneuropathy; DSP: distal sensory polyneuropathy; TDSP: toxic distal sensory polyneuropathy). Adapted from Gherardi et al (1998) (20).

rological symptoms in some patients with DSP, as suggested by occasional case reports (30).

Amyotrophic lateral sclerosis. Two recent articles described HIV-infected patients with an amyotrophic lateral sclerosis (ALS)-like disorder of rapid course, affecting both lower and upper motor neurons, and remarkably responsive to antiretroviral therapy (34, 29), suggesting that HIV-1 itself might have played a direct neuropathogenetic role (24). Six of 7 patients were younger (mean age: 34 years) than usually observed in ALS, as were the 9 previously described HIV-infected patients with ALS. The 6 patients reported by Moulignier et al (33) were identified during a 13-year period among 1700 HIV-infected patients with neurological symptoms, yielding a frequency exceeding the expected incidence of ALS in the general population (33). At onset, all patients were immuno-suppressed and had highly positive markers of CNS HIV infection, including CSF p24 antigen level and HIV viral load. Stabilization or complete remission of neurological symptoms was observed after successful treatment of HIV-1 infection (29, 33). HIV RNA became undetectable in CSF following neurological improvement in 3of 3 tested patients (29, 33). In 2 patients, reappearance of ALS symptoms was observed subsequently to escape from anti-HIV therapy (33). The authors report that since introduction of HAART, they have no longer observed ALS disorder among treated HIV-1 infected individuals (33).

The Role of Antiretroviral Drugs in Peripheral Nervous System Involvement

Antiretroviral agents introduced in recent years have shown both marked efficacy against HIV infection and significant side effects that often led to reduction in the recommended dose or duration of administration. Mitochondrial toxicity underlies most of these side effects, including myopathy, peripheral neuropathy, pancreatitis, hepatic steatosis, bone marrow suppression, lactic acidosis and, possibly, lipodystrophy.

Antiretroviral drugs mainly include nucleoside-analogue reverse-transcriptase inhibitors (NRTIs: zidovudine (AZT), stavudine (d4T), didanosine (ddI), zalcidabine (ddC), lamivudine (3TC), and fialuridine (FIAU)), non-nucleoside-analogue reverse trascriptase inhibitors (NNRTIs: nevirapine, delaviridine, efavirenz) and protease inhibitors (PIs: saquinavir, ritonavir, indinavir, nelfinavir, amprenavir).

Among reverse transcriptase inhibitors, only NRTI (nucleoside analogues) have been associated with peripheral neuropathy (11). Nucleoside analogues act in their tri-phosphorylated form through competition with the natural substrates of both HIV reverse transcriptase and γDNA polymerase, an enzyme involved in mtDNA replication (3, 4, 28). Some NRTIs, such as zidovudine, stavudine and fialuridine, are preferentially phosphorylated in replicating cells. Others, such as didanosine, zalcidabine and lamivudine, are replicated in resting cells (11). Phosphorylation of each NRTI may be selectively achieved by specific cellular thymidine kinase isoforms, the expression of which may vary from one tissue to another, thus explaining the remarkable tissue selectivity of NRTI-induced tissue toxicity (28). Zidovudine has long been recognized to induce a mitochondrial myopathy with ragged-red fibers and myofibrillar loss, partial cytochrome-c oxidase deficiency, mtDNA depletion and elevated lactate/pyruvate ratio in blood (2, 7, 8, 13, 32). Unlike other NRTIs, zidovudine is not toxic for peripheral nerve (27). In sharp contrast, all NRTIs except zidovudine may exert dose-dependent neurotoxic effects, ddC being more toxic than ddI, d4T and 3TC and the combination of ddI+d4T being more toxic than ddI or d4T alone (11). NRTI-induced neuropathy may be favoured by pre-existing sub-clinical PNS involvement and is clinically virtually undistinguishable from HIV-associated DSP. Temporal relationship between neurotoxic NRTI administration and onset or worsening of DSP, and improvement of clinical and electrophysiological signs of neuropathy after NRTI withdrawal or dose reduction may assess NRTI-induced DSP. However, one must be aware of the so-called "coasting" phenomenon that consists in temporary (2-4 weeks) worsening of symptoms after discontinuation of NRTIs followed by clinical improvement (11). When performed, nerve biopsy shows axonal loss affecting predominantly unmyelinated fibres (12, 28) (Figure 1E-F). Since ddC, similar to other nucleoside analogues, exerts in vitro toxicity to mitochondria (4), studies have looked for mitochondrial changes in peripheral nerve of animal models or patients with ddC neuropathy. In rabbits, ddC given at high doses was primarily toxic to the Schwann cells which exhibited mitochondrial alterations (17). In patients with ddC neuropathy, ultrastructural mitochondrial abnormalities were detected in both axoplasm and Schwann cells and were much more frequent than in HIV-associated DSP and other axonal neuropathies (14). These abnormalities were associated with marked decrease of the mtDNA content, as assessed by competitive PCR. These findings led to the consideration of ddC-neuropathy as a "mtDNA-deplet-

ing neuropathy" (11) by reference to the "mtDNA-depleting myopathy" caused by AZT (2).

HAART consists of a combination of two NRTIs and one or more PIs. The latter is considered non-toxic for peripheral nerve. However, one of the main toxic consequences of HAART is a lipodystrophy syndrome characterized by distal fat wasting contrasting with central adiposity, hyperlipidemia and insulin resistance (5, 6). It was not observed in patients receiving NRTIs only, suggesting that PIs may play a role in its causation possibly through a mechanism of mitochondrial toxicity. Indeed, the HAART-related lipodystrophy resembles multiple symmetrical lipomatosis syndrome (Launois-Bensaude or Madelung's syndrome) which is associated with mtDNA point mutations or deletions impairing cytochrome-C oxidase activity (5).

Conclusion

Introduction of highly active antiretroviral therapy has dramatically modified the course and prognosis of HIV infection and resulted in an improved quality of life for the patients. When considering involvement of PNS, these treatments have resulted in a marked decrease in the incidence of the peripheral neuropathies related to HIV-1, particularly DILS-associated neuropathy, DSP and HIV-1 associated ALS. Improvement of neurological signs was also reported in affected patients receiving HAART. On the other hand, the incidence of toxic neuropathies, which seem mainly related to anti-retroviral nucleoside analogues, is increasing with longer patient survival, and represents a major factor in treatment limitation.

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