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Role of HIV in the pathogenesis of distal symmetrical peripheral neuropathy

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Abstract We report the results of a clinical, electrophysiological and pathological study conducted in 18 AIDS patients presenting a distal symmetrical predominantly sensory polyneuropathy (DSPN) characterized by painful dysesthesias as main complaint. Onset of the neuropathy was at CDC (Center for Disease Control) stage II in 2 patients, at CDC stage III in 5 patients and at CDC stage IV in the remainder. Electrophysiological investigation confirmed the presence of an axonal alteration in the sensory nerves, but also revealed motor involvement in all cases. The neuropathological features of sensory nerves were fiber loss and axonal degeneration with macrophagic activation. The expression of monocyte-macrophage markers and of major histocompatibily complex class II antigens appeared up-regulated in endoneurial ramified cells, while expression of CR3, a complement receptor involved in the process of phagocytosis, was down-regulated. In six nerve biopsy samples and in two out of five DSPN dorsal root ganglia we found HIV-related mRNA and protein located in scattered cells of the endoneurium which we presume to be macrophages. These data suggest that: (a) DSPN may occur early in the course of the disease and is not limited to later stages; (b) DSPN is not a ganglionitis but is actually a sensory-motor neuropathy; (c) the virus enters the peripheral nervous system and induces changes in the immunocompetent cell population with activation of macrophages. Storage of the virus inside macrophages may act both as a reservoir for the virus and as a putative cause of nerve damage, probably through release of cytotoxins and/or interaction with trophic factors.

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Introduction

Peripheral neuropathy is a common neurological complication occurring in the asymptomatic or symptomatic stages of HIV infection. Several types of neuropathy have been described according to their clinical, electrophysiological and pathological features [2, 5, 16, 19]. The most frequent and distinctive syndrome, usually associated with the late manifestations of the infection, is a distal symmetrical predominantly sensory polyneuropathy (DSPN) with painful dysesthesias as the main symptom [13, 14]. The disease affects 10–30% of HIV-infected subjects [6, 28]. The mechanisms of nerve damage are still unknown.

The purpose of this study was to review the clinicopathological findings in a series of 18 HIV-positive patients with DSPN and to investigate the pathogenesis of peripheral nervous system (PNS) involvement. The demonstration of HIV transcripts and protein in the cytoplasm of macrophages, in the endoneurium of the sensory nerves and in the dorsal root ganglia (DRG), together with evidence of macrophage activation, suggest that the virus itself might play a role in the nerve damage mechanism.

Materials and methods

Patients

Eighteen patients with HIV-1 infection and signs and symptoms of PNS involvement were referred to our department for clinical and electrophysiological evaluation and for sural nerve biopsy (Table 1). All but two of these patients (nos. 14 and 18) were drug addicts. Patients were carefully investigated to rule out any other condition that might have led to a neuropathy. Ten patients (nos. 2, 5, 8, 10, 12, 13, and 15–18) received a standard dosage (300 mg/day) of zidovudine (AZT); none were treated with dideoxyinosine (ddI).

Electromyography (EMG) and measurement of motor and sensory nerve conduction velocities were performed according to routine procedures. Autopsy samples of lumbosacral DRG from ten

AIDS patients were given to us by Dr. P.L. Gambetti (Division of Neuropathology, Case Western Reserve University, Cleveland, Ohio); five were from HIV-positive patients with DSPN, the others from AIDS patients without any signs or symptoms of peripheral neuropathy.

Tissue processing

Sural nerve biopsy

Sural nerve samples were taken at the level of the lateral malleolus. The specimens were processed for histological, ultrastructural, and teased fibers examination following the standard protocol of our laboratory [3]. For immunohistochemistry (IHC) and in situ hybridization (ISH), nerve samples were snap-frozen in liquid nitrogen.

Autopsy samples of dorsal root ganglia

DRG samples were fixed in formalin and embedded in paraffin; 5- to 8-μm-thick sections were cut for histology, IHC and ISH.

Morphometric analysis

The quantitative analysis was done on micrographs, printed at × 1000 final magnification, of three randomly chosen fields of each nerve. The total number and density of the myelinated axons were counted; D-circles (diameters of circles with an equivalent area) of 800–1000 myelinated fibers were measured using the Videoplan Kontron System. Axonal diameters were plotted at 1 μm intervals according to their frequency distribution. Histograms of fiber diameters were obtained.

Immunohistochemistry

For immunocytochemical investigation, a previously published protocol of our laboratory was used [3]. Briefly, direct immunofluorescence on frozen sections of peripheral nerve was performed using fluorescein-conjugated polyclonal antibodies recognizing human immunoglobulins, light chains and the complement components C1q, C3d and C5 (Dako, Glostrup, Denmark).

Avidin-biotin immunoperoxidase staining was performed on frozen sections of nerves and on paraffin sections of ganglia with the following monoclonal antibodies: KP1 (Dako), which recognizes CD68 antigen (1:3200), and HAM56 (Enzo Biochem, New York, NY) as markers of the monocyte-macrophage population (1:30); L26 and UCHL1 (Dako) antibodies reacting with CD20 and CD45RO antigens as markers for B and T cells, respectively (1:200, 1:200), and LN3 (Clonab, Dreieich, Germany) recognizing HLA-DR molecules (1:10).

On frozen nerve sections additional markers were used: RM3/1 (BMA, August, Switzerland) directed against an undesignated macrophage antigen (1:400), Leu-4 (Becton Dickinson, Mountain View, Calif.) recognizing the complement receptor type 3 (CR3; 1:10), D1.12 [1] which reacts with HLA-DR antigens (1:6400) and MT310 (Dakopatts, Glostrup, Denmark), an antibody labeling the CD4 antigen (1:400).

A monoclonal antibody recognizing the HIV-1 p24 core protein (Dako; 1:20) was used on cryostatic sections of 13 nerve biopsies.

In situ hybridization

Sequences corresponding to the Pol (*Eco*RI fragment of 1100 bp) and Gag (*Pst*I fragment of 800 bp) regions of the HIV BH10 clone (kindly provided by Dr. Gallo [24]) and a sequence corresponding to transforming region PCM 400 (*Bam*HI/*Hin*dIII fragment of 598 bp) of cytomegalovirus (CMV) AD169 clone [21] were used as template for riboprobe transcription.

Sense and antisense RNA probes were obtained by linearization of the pBSK+ (Stratagene, La Jolla, Calif.) constructs and transcribed from the T3 or T7 promoters, using [^{35}S]UTP (Amersham, Buckinghamshire, UK) to give RNA transcripts with a high specific activity (approximately 1×10^8 cpm/μg DNA template). ISH was performed on frozen sections of 13 peripheral nerve biopsy samples and on paraffin sections of all ganglia, as previously described [4]. The ^{35}S-labeled mRNA probe had a final activity of 3×10^6 cpm/μl and hybridization was performed overnight at 50°C. Sections were dipped in NTB2 (Kodak, Rochester, NY) emulsion and stored in the dark for 3–4 weeks, and then developed in D19 solution (Kodak). Slides were counterstained with hematoxylin-eosin, mounted and viewed under a light microscope.

Results

Clinical and electrophysiological features

Of the 18 patients, 12 had a sensory neuropathy with painful paresthesias in the lower limbs as the main symptom; 4 of these (nos. 5, 6, 10 and 18) showed a mild sensory ataxia (Table 1). According to CDC (Center for Disease Control, Atlanta, 1986) criteria, the onset of the neuropathy occurred at stage II in 1 patient, at stage III in 5 patients, and at stage IV in 6 patients (Table 1).

Six patients (nos. 7, 8, 13 and 15–17) had a distal symmetrical sensory and motor neuropathy mainly involving lower limbs, with pain as the main complaint; at the onset of the neuropathy, 1 patient was in stage II and 5 were in stage IV (Table 1).

Despite the predominance of sensory symptoms, all 18 patients showed symmetrical involvement of both sensory and motor nerve conduction. The main finding was a reduced amplitude of the evoked responses with normal or slightly decreased conduction velocity. Sensory responses of the sural nerve were severely reduced in amplitude in 12 patients and absent in the other 6. Motor conduction studies showed a variable reduction of the evoked response amplitude in all patients and a slowed peroneal nerve motor conduction velocity in 4 patients (35–40 m/s). There was no evidence of conduction blocks. These abnormalities had a symmetrical distribution.

EMG demonstrated a reduced recruitment with a significant component of polyphasic potentials (30%) during maximal voluntary effort in the distal leg muscles. Spontaneous activity, consisting of sharp waves and fibrillation potentials in foot muscles, was detected in 1 patient. None of the patients showed EMG signs of reinnervation of motor units. These findings were unchanged in 5 patients (nos. 1, 3, 9, 10 and 14), retested after 6 and 18 months.

Thus, in our cases, the clinical and electrodiagnostic results were consistent with a distal symmetrical polyneuropathy, with prevalent axonal involvement.

Nerve biopsy findings

Light microscopic examination of semithin sections disclosed a variable loss of myelinated fibers, with signs of

Table 1 Clinical and electrophysiological findings in AIDS-associated distal, symmetrical, predominantly sensory neuropathy

Case no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Age (years)/sex	33/M	32/F	31/M	29/M	29/M	29/F	33/M	26/M	28/M	38/M	27/M	32/M	27/M	54/F	28/M	26/F	43/M	48/M
CDC group	III	III	III	III	IV	IV	II	IV	III	IV	IV	IV	IV	II	IV	IV	IV	IV
AZT treatment (300 mg/day)	no	yes	no	no	yes	no	no	yes	no	yes	no	yes	yes	no	yes	yes	yes	yes
Distal weakness	+/–	+/–	+/–	+/–	+/–	+/–	++	++	+/–	+/–	+/–	+/–	++	+/–	++	++	++	+/–
Pain paresthesias	++	++	+++	++	+++	++	+/–	++	+++	+++	+++	+++	+++	++	+++	+++	+++	+++
Sensory deficit	+	+	–	+	++	+	–	++	–	+	+	+	–	+	–	–	++	++
Gait ataxia	–	–	–	–	++	++	+	–	–	++	+	–	–	–	+	+	+	++
NCS	Mx	A	A	A	A	A	Mx	Mx	A	A	Mx	A	A	A	A	A	A	A

[*AZT* zidovudine, – absent, +/– light, + mild, ++ moderate, +++ severe, *NCS* nerve conduction study, *A* axonal, *Mx* mixed (axonal-demyelinating)]

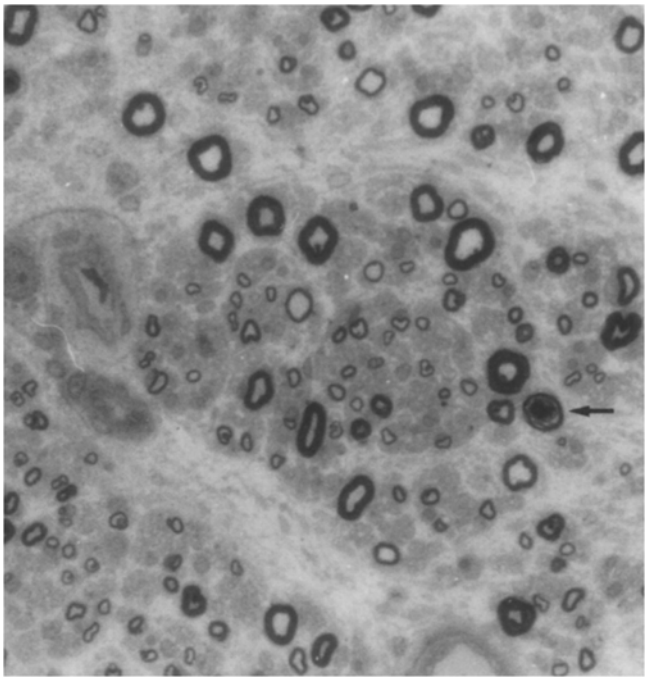

Fig. 1 Loss of myelinated fibers with scattered axonal degenerations (*arrow*). Semithin sections, toluidine blue, × 480

ongoing axonal degeneration (Fig. 1). Demyelination were absent in the majority of nerves; a few clusters of regeneration and/or segmental remyelination were present in cases 1, 3, 6, 7, 9 and 18 (Table 2).

Quantification of the fiber density revealed values ranging from 2520 to 5330/mm^2 (controls 6000–10000/mm^2). The histogram of the myelinated axons was shifted to the left, indicating a preferential involvement of the fibers with larger diameter and/or axonal atrophy; the histograms showed a normal bimodal pattern in only two cases (nos. 2 and 14).

Denervated Schwann cell profiles and collagen pockets were variably present in all cases, but the amount of unmyelinated axon loss was proportional to the loss of myelinated fibers. No tubuloreticular inclusions or intracellular profiles similar to those described after prolonged stimulation with interferon were found in lymphomonocytes, macrophages or endothelial cells. No immunoglobulins, complement deposits or inflammatory infiltrates were found.

Immunostaining with CD68, HAM56 and RM3/1 revealed a population of resident immunocompetent macrophages with an elongated and ramified morphology (Fig. 2 A), which also exhibited a CD4 reactivity. When compared to normal controls [3], these macrophages appeared morphologically and phenotypically activated; they were

Fig. 2 **A** Immunohistochemistry (IHC) with CD68 antibody: activated macrophages (*arrow*). **B** IHC with D1.12 antibody: resident macrophages expressing HLA-DR molecules (*arrow*). **C** IHC with Leu-4 antibody: faint reactivity of resident macrophages to the complement receptor type 3 (*arrow*). **A–C** Frozen sections, avidin-biotin, × 360 ▶

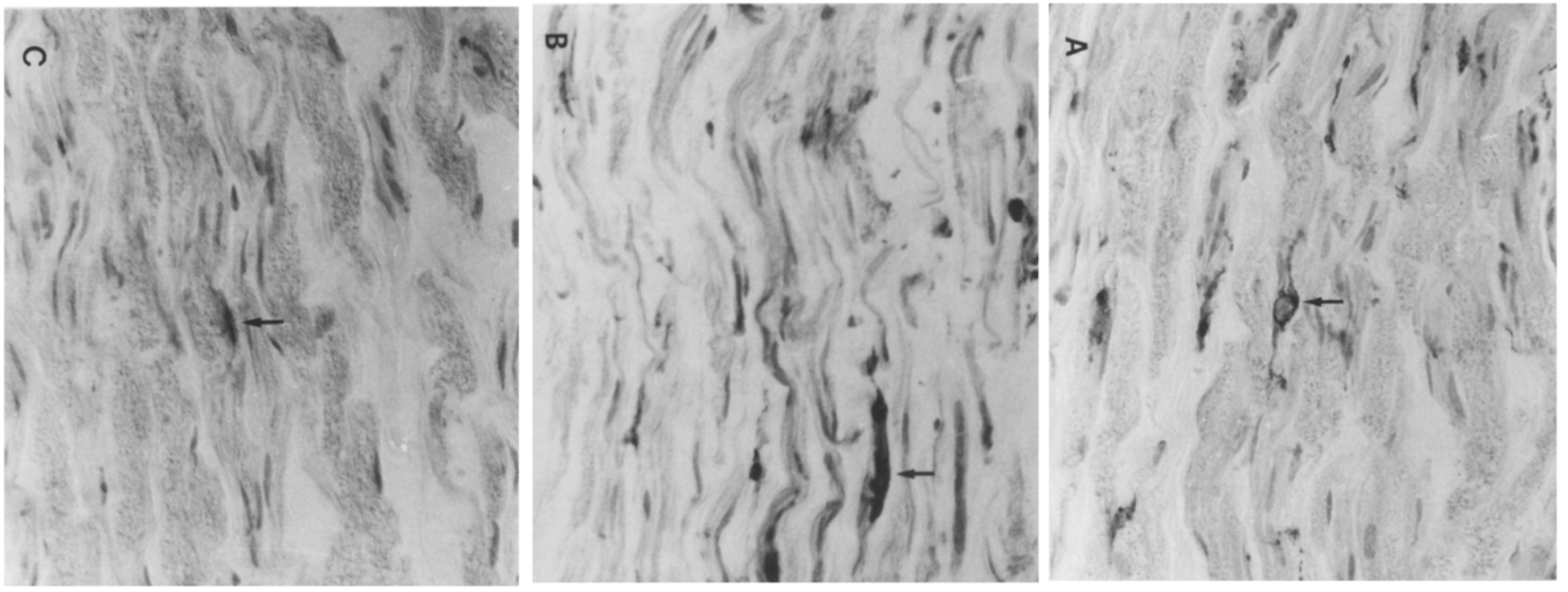

Table 2 Pathological findings of peripheral nerve biopsies

Case no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Fiber density (MF/mm^2)	3500	3720	3570	4400	2520	2550	4740	4976	3275	2780	2715	3530	5283	5206	3740	5330	3645	3260
Axonal degeneration	++	+	+	+	+++	++	+	+++	+	+++	+++	+	+	+/–	++	+/–	+++	+++
Regeneration clusters	+	–	+	–	–	+	+	–	+	–	–	–	–	–	–	–	–	–
Demyelination	–	–	–	–	–	–	+	–	–	+	–	+/–	+	+/–	–	–	–	–
Remyelination	+	–	+	–	–	+	+	–	–	–	–	–	–	–	–	–	–	+/–
HIV α24 (IHC)	–	–	–	–	–	+	+	ND	+	+	–	–	+	+	ND	ND	ND	ND
HIV mRNA	–	–	–	–	–	+	+	ND	+	+	–	–	+	+	ND	ND	ND	ND
CMV mRNA	–	–	–	–	–	–	–	ND	–	–	–	–	–	–	ND	ND	ND	ND

(*MF* myelinated fibers, *IHC* immunohistochemistry, *CMV* cytomegalovirus, – absent, +/– occasional, + present, ++ moderate, +++ severe, ND not done)

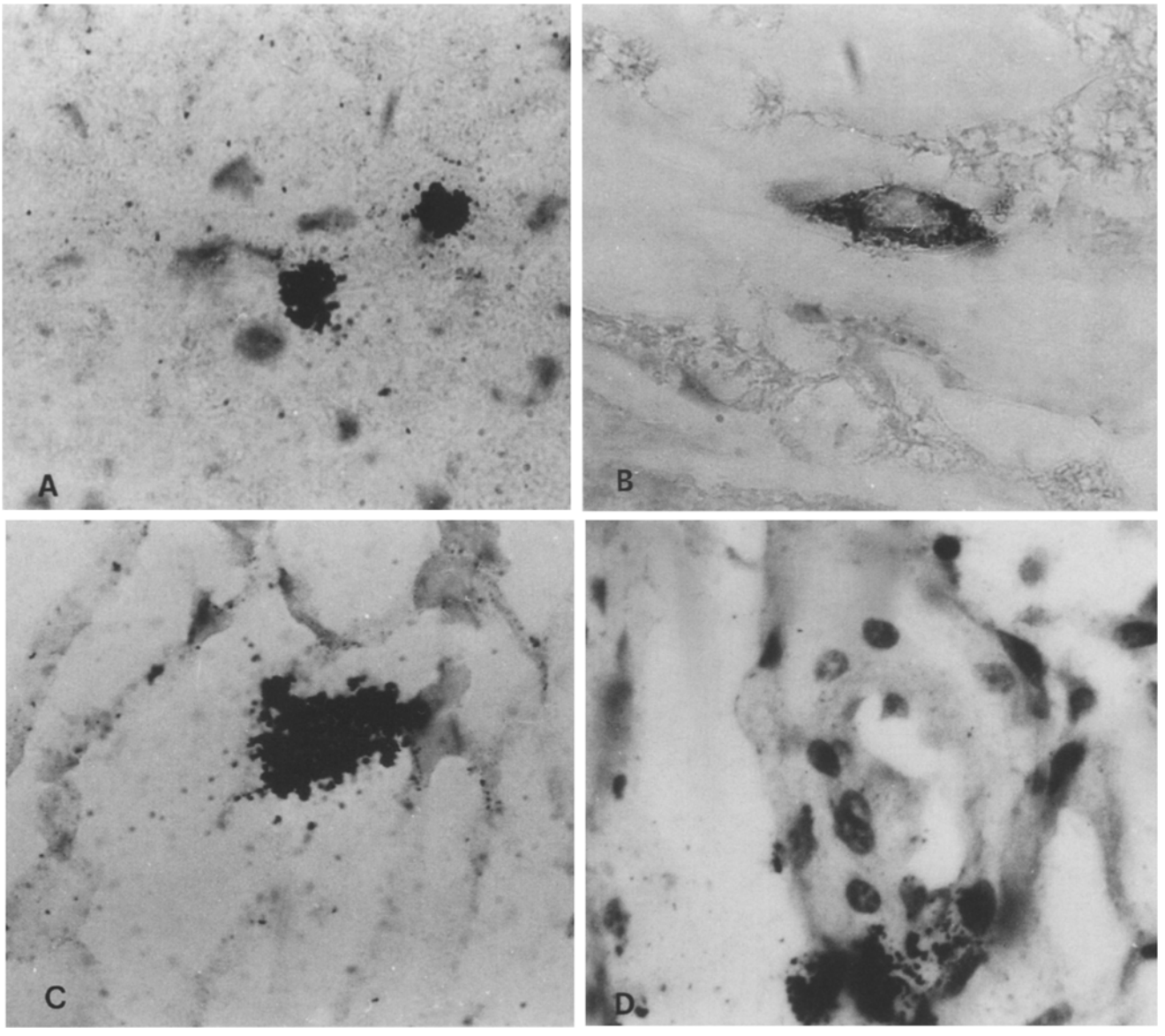

Fig. 3 **A** Endoneurial cells labeled with HIV mRNA probe: note the intense positive signals. Frozen section. **B** Immunostaining of an endoneurial cell with HIV p24 core protein antibody. Frozen section, avidin-biotin. **C** HIV-positive signals in a macrophage element in dorsal root ganglia (DRG). Paraffin section. **D** cytomegalovirus-positive element in perivascular location in DRG. Paraffin section. **A–D** × 1200

increased in number, with fewer ramifications, and showed an up-regulation of HLA-DR antigens (Fig. 2 B) and of most macrophage markers. By contrast, a very faint CD3 reactivity with only a few irregularly immunostained cells was observed in all biopsy samples (Fig. 2 C).

ISH showed strong positive signals for the HIV transcripts inside scattered endoneurial cells (Fig. 3 A), presumably macrophages, in samples from patients 6, 7, 9, 10, 13 and 14 (Table 2). In these cases ISH did not reveal any HIV transcript in axons and in Schwann cells. IHC confirmed the presence of HIV-related proteins (Fig. 3 B) in the same cases in which HIV mRNA transcripts were detected (Table 2). In none of the nerve biopsy samples did ISH provide evidence of CMV transcripts.

Dorsal root ganglia findings

Histological examination of all DRG showed a slight reduction in the number of sensory neurons associated with nodules of satellite cells (nodules of Nageotte). No perivascular inflammatory foci were found in either the ganglionic connective tissue or the DRG themselves. IHC analysis revealed proliferation of macrophages (HAM56 positive) often localized around sensory neurons. In the same cases we noticed an increase in T cells which were dispersed through the ganglia. B cells were rarely found. There was no immunophenotypical difference in ganglia between HIV-positive cases with and without DSPN.

In two cases with PNS involvement, ISH revealed HIV transcripts in a few monocyte-macrophage cells (Fig. 3 C).

In the same cases CMV-related transcripts were evident in endothelial and perivascular macrophages (Fig. 3D).

Discussion

Painful neuropathy (DSPN) represents the most common disorder of the PNS affecting patients in the late stages of HIV infection [6]. Its pathogenesis is still unclear. A toxic action of AZT and a dysmetabolic mechanism due to chronic malnutrition have been suggested to play a role in the pathogenesis [7]. However, in our series of 18 patients, DSPN affected 7 patients in early stages of the disease, when deficiency-related conditions and wasting were not yet present. Moreover, no differences in the severity of the clinical, electrophysiological or morphological features were detected between AZT-treated and untreated patients. Therefore, we believe that the toxic-metabolic hypothesis does not fully explain the pathogenesis of DSPN.

Due to the prevalence of sensory symptoms, DRG are thought to be primarily affected in DSPN [11, 23, 27]; however, the precise site of PNS involvement is still a matter of debate. Our data are not consistent with the hypothesis of a mere ganglionitis: in fact, even though the clinical picture was predominantly that of a sensory neuropathy, all patients exhibited electrophysiological evidence of both motor and sensory abnormalities, thereby suggesting that this entity is a true mixed sensory-motor neuropathy. Thus, our clinical and electrophysiological findings indicate that the peripheral nerve may actually represent a candidate site of the pathological process.

HIV is known to play a direct role in the peripheral neuropathy associated with necrotizing vasculitis [15]. By contrast, in DSPN, evidence of HIV presence in peripheral nerve is limited to a few occasional reported cases [18, 32]. The combined application of ISH and IHC to our relatively large DSPN-series provides evidence for a possible pathogenetic role of the virus by allowing the detection of HIV transcript and antigen in scattered cells of endoneurium and endoneurial septa in 6 out of 13 nerve biopsy samples examined. Remarkably, they were always absent in the axons and Schwann cells. The absence of HIV-related signals with ISH in 7 nerve biopsies can be explained by the difficulty of detecting the low number of virus copies in the early stages of the disease.

CMV is involved in two other HIV-related neuropathies, characterized respectively by multifocal inflammatory and necrotic lesions [26] and by demyelinating polyradiculoneuropathy [9, 20]. Based on the observation of an increased serum titer of CMV antibodies in DSPN patients, a role of this virus in the neuropathy has been proposed [12]; however, we have not detected any CMV transcripts in the peripheral nerves of our patients.

Since IHC did not reveal any T cells, and the only CD4-positive elements in the endoneurium were morphologically similar to the resident immunocompetent population, it is reasonable to assume that macrophages are the cellular targets of HIV infection. Resident macrophages represent a widely distributed cellular system displaying various physiological and pathological functions [3, 17, 30]. They are activated in a large group of neuropathies, undergoing hypertrophic, hyperplastic, and possibly, phagocytic changes.

Macrophage activation was present in all of the DSPN nerve biopsy samples but, in contrast with what is observed in inflammatory neuropathies, in our cases they were not associated with perivascular cuffing and/or immunoglobulin or complement deposition. We cannot, however, exclude that an inflammatory response with production of cytokines and interferons had occurred earlier in the evolution of the neuropathy. Despite their hyperplastic and hypertrophic features, macrophages showed a distinct down-regulation of CR3 in DSPN. Since CR3 is involved in the process of phagocytosis, this immunophenotypical modulation reflects a selective dysfunction of the infected macrophages with an impairment of the phagocytic functions. CR3 in lymphomonocytic cells has been proposed as a port of entry for HIV into cells as an alternative to CD4 receptors [29]. The CR3 down-regulation may be the marker of a more direct involvement of these receptors in HIV infection. The route of entry of the virus can only be speculated on: the turnover of resident macrophages from blood monocytes occasionally provides an opportunity for the entry of infected monocytes into both nerves and ganglia [11].

Similar to the mechanisms hypothesized for CNS pathologies such as AIDS-dementia complex [22, 33] and vacuolar myelopathy [31], HIV-infected macrophages may induce nerve changes by interacting with the production of trophic factors and/or promoting a release of cytotoxins [33].

To confirm that DRG do not represent the primary site of the pathological alteration in DSPN, morphological, ISH and IHC analyses were also performed on lumbar ganglia from patients affected with DSPN and HIV-positive patients without peripheral nerve involvement. No differences in histological features and immunophenotypical characterization of lymphomonocytic cells were detected between the two groups. A few macrophages showed the presence of HIV and CMV transcripts in only two cases with DSPN. These data suggest that the involvement of DRG alone cannot explain the development of DSPN.

Absence of CMV in all DSPN nerves and in three out of five DSPN ganglia indicates that this virus represents an occasional finding in PNS; when present it may play a synergistic role with the HIV.

In conclusion, we have shown that DSPN is not a mere ganglionitis, but rather reflects an involvement of motor and sensory fibers. HIV-infected macrophages resident in peripheral nerve are the primary candidate of pathogenicity. They could act both as a reservoir for maintaining the infection and as releasers of cytokines, thus amplifying the immunomediated damage. Finally, the hypothesis of macrophages behaving as the "Trojan horse" [10] for CNS pathology in HIV infection may also apply to PNS.

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