The spectrum of polyneuropathies in patients infected with HIV

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SUMMARY Twenty five patients with peripheral neuropathy at different stages of human immunodeficiency virus (HIV) infection are reported. Cerebrospinal fluid (CSF) findings were available in 17 cases, electrophysiology in all and a neuromuscular biopsy in 11. Of six otherwise asymptomatic HIV+ patients, five had chronic inflammatory demyelinating polyneuropathy (CIDP) and one acute inflammatory demyelinating polyneuropathy (AIDP). CSF showed pleocytosis in all cases. Infiltration of the endoneurium and/or the epineurium by mononuclear cells was seen in biopsies from three cases. These six patients recovered either spontaneously, or with corticosteroids or plasmaphereses. Of five patients with AIDS related complex (ARC), three had distal predominantly sensory peripheral neuropathy (DSPN), one CIDP and one mixed neuropathy. Of 14 patients with AIDS, one had mononeuropathy multiplex and 13 painful DSPN. Electrophysiological studies were consistent with an axonopathy. Nerve biopsies in six cases showed axonal changes but surprisingly associated with marked segmental demyelination in two cases. Cell infiltration was present in nerve samples in two cases. Five patients died within six months after the onset of the neuropathy.

Various disorders of the peripheral nervous system associated with HIV infection have been reported. In nine to 16% of patients with AIDS and 20% of patients with ARC their incidence has probably been underestimated. Some recent reviews have tried to classify peripheral neuropathies and other muscular complications.*,†,‡,§ On the other hand, de la Monte et al did not distinguish between the neuropathy of AIDS and the neuropathy of ARC and suggested that these syndromes be regarded as the same disease process with variable expression. We report clinical, electrophysiological and pathological findings in 25 patients who manifested a peripheral neuropathy at different stages of HIV infection.

Patients

From November 1984 to June 1988, 25 patients with HIV infection and a peripheral neuropathy were referred to the Neurological Department and the Department of Parasitology and Tropical Medicine at Salpêtrière Hospital; 18 patients were known to be seropositive before admission (for a period of from 1 to 48 months); the other seven were found to be seropositive during their admission to hospital for the neuropathic disorder.

Methods

Information included the following: age, sex, risk factor for HIV infection, duration of HIV infection and characteristics of the peripheral neuropathy. Follow up studies were conducted over a period of one month to four years.

Laboratory investigations

Serum specimens were analysed for the antibody to HIV1 by enzyme-linked immunosorbent assay, and positive sera were confirmed by Western blots. Peripheral blood CD4/CD8 ratio was available in 20 cases. CSF cellularity, protein and glucose levels were obtained in 17 cases.

Electrodiagnostic studies included examination with concentric needle electrode and nerve conduction velocities in all cases. Motor nerve conduction velocities were determined on peroneal and median nerves by surface electrodes. Sensory nerve action potential amplitude and conduction velocities were determined on sural and median nerves by near-nerve needle electrodes. Criteria for demyelinating neuropathies
were those defined by Kelly.\textsuperscript{5} Electrodagnostic studies were repeated in six cases. A neuromuscular biopsy was performed on 11 patients. The peroneus brevis muscle and the cutaneous branch of the superficial peroneal nerve were removed for examination; specimens from nerve and muscle, after embedding in paraffin, were stained by hematoxylin and eosin and Masson’s trichrome and examined with light microscopy. For morphometric study, semithin sections (2 μm thick) of nerve were embedded in Epon 812 and stained with toluidine blue. The size and density of myelinated fibres per 2 mm of endoneurial area were determined by using a semi-automatic analyser ASM Leitz. For the preparation of teased nerves, 10 mm length specimens were fixed by 2.5% glutaraldehyde in 0.1 cacodylate buffer pH 7.4 for 24 hours, post-fixed in 2% osmium tetroxide and embedded in Epon 812.

Results

Clinical and laboratory features are reported in table 1. The 25 patients were: 23 white males, one black female and one black male ranging from 27 to 58 years; of the 24 males, 20 were homosexual/bisexual and four were former intravenous drug users. Six were otherwise asymptomatic seropositive patients; 14 patients had AIDS as defined by the Centers for Disease Control’s criteria,\textsuperscript{10} and five had ARC characterised by seropositivity for HIV, lymphadenopathy, and the absence of opportunistic infections or neoplasia. The CD4/CD8 ratio in peripheral blood was reduced in 16

Table 2 Electrophysiological features in polyneuropathies of HIV-infected patients

<table>
<thead>
<tr>
<th>No of cases</th>
<th>AS/ARC/AIDS</th>
<th>Fib potent</th>
<th>MCV median (ms)</th>
<th>DL (ms)</th>
<th>MCV peroneal (ms)</th>
<th>DL (ms)</th>
<th>SCV median (ms)</th>
<th>Amp (μv)</th>
<th>SCV sural (ms)</th>
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<tr>
<td>0-6 months</td>
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<td>0-48 months</td>
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</table>

Normal: mean (SD) of 40 normal subjects.
Fib potent: Fibrillation potentials; MCV: Motor conduction nerve velocities; SCV: Sensory conduction nerve velocities; DL: Motor distal latencies; AS: asymptomatic; Amp: Amplitude;
patients (less than 0·9) and normal in four.

**Group 1:**
The first group was made up of six otherwise asymptomatic patients (table 1) who had an inflammatory demyelinating polyneuropathy (IDP) with symmetrical proximal and distal weakness, relatively mild sensory symptoms and generalised areflexia. None had other systemic manifestations, but patients 3 and 5 had a progressive encephalopathy, with normal brain CT. Patient 4 had an acute evolution resembling the Guillain-Barré syndrome, requiring a tracheotomy and assisted ventilation. Patients 1, 2, 3, 5 and 6 had a progressive evolution characteristic of chronic inflammatory demyelinating polyneuropathy (CIDP). CSF was examined in all cases: the total protein concentration ranged from 98–400 mg/100 ml, and the leucocyte count ranged from 7–71 cells/mm³.

**Electrodiagnostic studies (table 2)** Motor nerve conduction velocities (MCV) were considerably reduced in the lower limbs in all six cases (especially in case 1) and in the upper limbs in three cases. Distal motor latencies were prolonged in the four limbs in all cases. Muscle action potentials (MAP) were increased in duration in five cases, normal in case 6. Sensory potentials were abnormal in all cases. Fibrillation potentials at rest were found in patient 4 later in the course of the disease. A biopsy was performed on four patients (results are given below).

**Evolution** The 6 patients recovered: patients 2, 3, 5 and 6 recovered spontaneously, patient 1 responded to corticosteroids and the only patient with acute IDP (case 4) had four plasmaphereses. Repeated electrophysiological examinations in three patients showed a dramatic improvement of MCV, motor DL and sensory potentials corresponding to the clinical improvement. The follow up of patients 1, 2, 3, 4 and 5 was conducted from one to four years: they have all progressed to ARC but none has progressed to AIDS.

**Group 2:**
The second group was made up of five patients with ARC (table 1). The duration of the HIV infection, before the first symptoms of the peripheral neuropathy appeared, ranged from three to 16 months. All patients complained of paresthesias of the lower extremities; paresthesias of the upper extremities were present in cases 8, 10 and 11. Neurological examination showed a distal motor weakness of the lower limbs in cases 7 and 9, a distal and proximal weakness of the lower limbs in case 10. Position and pain sensations were diminished in the lower extremities in all cases and in the upper extremities in cases 8, 10 and 11. The ankle jerks were absent in cases 7, 9 and 10, diminished in the two other cases. CSF examined in case 7 was normal.

**Electrodiagnostic studies (table 2)** A neurogenic pattern (reduced interference pattern at full voluntary contraction) was found in the distal muscles in all cases. No myopathic patterns were present. MCV were consistent with a chronic IDP in case 10, an axonopathy in cases 7, 8 and 11, and a mixed axonal-demyelinating polyneuropathy in case 9 (which was confirmed in nerve biopsy). Sensory potentials were diminished in amplitude in the upper limbs in four cases and absent or diminished in amplitude in the lower limbs in all cases.

**Evolution** Follow up studies were conducted over periods of from six to 24 months. Patients 7 and 9 died two years and 21 months later respectively, both probably of a subacute AIDS encephalitis, but the neuropathy was stable. Patients 8, 10 and 11 were unchanged 24, six and nine months later respectively. None progressed to AIDS.

**Group 3:**
The third group was made up of 14 patients with AIDS (table 1). The average duration of the disease before the first symptoms related to the peripheral neuropathy appeared, was 14·1 months (range: 0–48). All
had opportunistic infections (tuberculosis: 7, *pneumocystis carinii* pneumonia: 8, Toxoplasmosis: 3, cytomegalovirus (CMV) retinitis: 2) and four patients also had Kaposi's sarcoma. Slowly progressive dementia was present on a clinical basis in six cases. One patient had a mononeuropathy multiplex (case 12) and the electrophysiological features were consistent with an axonopathy (table 2). The 13 others complained of painful dysesthesias of the lower extremities. Dysesthesias of the upper extremities were present only in case 23. Neurological examination showed a distal sensory polyneuropathy in all cases: the ankle jerks were absent in 11 cases and reduced in two cases. The knee reflexes were absent in case 25. Only three patients presented a mild distal weakness in the lower limbs. CSF was examined in 10 cases and always found normal, except in cases 18 (leucocytosis) and 23 (protein elevation).

**Electrodiagnostic findings in DSPN** (table 2) On EMG examination, fibrillation potentials at rest were found in 1/9 patients. Nerve conduction studies were indicative of an axonopathy: MCV's were normal or slightly reduced in proportion to the reductions in amplitude (peroneal MCV abnormal in 10 cases and median MCV abnormal in three cases). Sensory potentials were abnormal mainly in amplitude: for the sural nerve, five patients showed no response, six had abnormal responses and two had normal responses. For the median nerve, there were six patients with abnormal responses and seven with normal responses.

**Evolution** Patient 12 with mononeuropathy multiplex was stable one year later. Patients 13, 14, 15, 16 and 24 died within six months. The nine other patients are alive at the time of this study, but the follow up has not exceeded one year. In two patients the neuropathy has worsened, particularly with the development of motor weakness.

**Nerve and muscle biopsies** (table 3: cases 1, 2, 4, 6, 9, 12, 13, 14, 16, 23, 24). Detailed reports on pathological findings in patients 1, 2, 4, 9, 12 and 13 will be published separately.

**Muscle biopsies** A denervation atrophy was seen in every case. A mononuclear cell infiltrate, as described below under nerve biopsy, was seen in the interstitium in five cases (1, 2, 6, 9, 13).

**Nerve biopsies** In cases 1, 2, 4 and 6 (asymptomatic seropositive patients with IDP) the density of myelinated fibres was normal or high in two cases and low (under 8650/mm²) in the two others. Teased fibre preparations showed significant segmental demyelination in all cases, associated with an axonal degeneration in three cases (which was accentuated in case 4, probably because the nerve biopsy was performed later in the course of the neuropathy). In cases 1, 2 and 6, infiltration of the endoneurium and/or the epineurium by mononuclear cells was seen; it was usually predominant around and in the walls of small vessels whatever the type, but never involved the walls of arteries with a diameter above 80 µm. No fibrinoid necrosis was seen. The cell infiltrate usually consisted of normal lymphoid cells and monocytes.

In case 9 (ARC), the density of myelinated fibres was quite normal, but teased fibre preparations showed mixed axonal-demyelinating changes consistent with the electrophysiological findings. Cell infiltrates were present in the endoneurium and the epineurium, with involvement of vascular walls of small vessels.

In cases 12, 13, 14, 16, 23 and 24 (AIDS with either mononeuropathy multiplex or DSPN) the density of myelinated fibres was very high in case 16 indicating a marked regeneration and low in the five others. Teased fibre preparations showed a predominantly axonal degeneration in four cases and a predominantly

<table>
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<th>No of cases</th>
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<th>Teased fibres</th>
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Table 3 Nerve and muscle biopsies
The spectrum of polyneuropathies in patients infected with HIV

segmental demyelination in two cases (23 and 24). Cell
infiltrates were found in cases 12 and 13 (where the
duration of the HIV disease was one and seven months
respectively) and absent in cases 14, 16, 23 and 24
(where the duration of the HIV disease was 16 months,
two years, 10 months and 21 months respectively).

Discussion

Peripheral nervous system (PNS) manifestations of
AIDS and ARC have become more and more widely
recognised, but there are relatively few papers on
the clinical features and the natural history of per-
ipheral neuropathy. Systematic electrophysiological
studies have been conducted in HIV patients and
have shown a high frequency of abnormalities.19-21 Nerve
biopsies11,22 have shown either axonal or demyelinating
changes, and frequent mononuclear cell infiltration
in the early stages of the HIV infection.

Based on clinical and laboratory criteria, several
distinct types of peripheral neuropathies have been
identified but questions persist regarding the correla-
tions with the HIV-infection stages and the electro-
physiological and pathological findings. In our study,
otherwise asymptomatic patients presented an inflam-
matory demyelinating polyneuropathy (IDP), mainly
subacute. These findings were strikingly similar to
those previously reported.13,18,23,24 Two features dif-
ferrentiate this type of neuropathy from common IDP:
CSF pleocytosis, associated with high protein level,
and inflammatory cell infiltrates in nerve biopsies. The
predominant cell type has been found to be CD8
positive.13 IDP occurs at relatively early stages of the
disease, before severe immunodeficiency, and proba-
ably results from immunopathogenic mechanisms
(macrophage-mediated demyelination) rather than
direct viral infection.13 In three other published cases,
IDP has been shown to be a symptom of HIV
seroconversion.25,26 For other authors, the presence of
cytomegalovirus (CMV) in the Schwann cells in
previously published cases of Guillain-Barré syn-
drome associated with HIV infection,28 increases the
likelihood that CMV may play a causative role in some
patients. IDP usually improves spontaneously with
corticosteroids or plasmaphereses13 but response to
treatment is not uniform and the absence of response
may be a sign of poor prognosis.7 In our series, the
long-term prognosis was good.

In ARC the spectrum of the peripheral neuropathy
was heterogeneous, usually distal symmetrical axon-
opathies, but also mixed axonal-demyelinating poly-
neuropathy and chronic IDP. Prognosis seems to be
worse than in otherwise asymptomatic patients. In our
series most patients failed to progress satisfactorily
and some of them developed AIDS. Four similarly
affected patients of Lipkin et al7 died less than one
year after the onset of the neuropathy. Five of six
patients reported by Cornblath et al8 later developed
AIDS (on average, 7 months later).

Of the AIDS patients in our study, only one showed
a multiple mononeuropathy. The clinical, electros-
physiological and pathological features of this case
were similar to those reported by Lipkin et al.18
Electrophysiological studies show more widespread
evidence of peripheral nerve disorder than expected
from the sensory symptoms alone, and nerve biopsy
specimens point to a severe axonopathy accompanied
by perivascular inflammatory infiltrates in most cases.
A second form of vasculitic-type multiple mono-
neuropathy has been reported by Said et al26 and
Lange et al.7 in nerve biopsies a necrotising vasculitis
similar to that seen when periarteritis nodosa was
present.

A predominantly sensory painful polyneuropathy
affected the other AIDS patients of our series. This
type of neuropathy was reported in the first publi-
cations3 and is probably the most common PNS
disease in HIV infection, affecting up to 30% of
patients with AIDS.29 It is associated with profound
immunosuppression and multiple opportunistic infec-
tions and sometimes malignancies. Seven of our
patients took isoniazid for a pulmonary or generalised
tuberculosis, but their neuropathy was no different
from those of other patients and had generally begun
before this treatment. The patients complain of pain in
their feet and present signs of distal symmetrical
peripheral neuropathy on clinical examination. CSF is
usually normal. Electrophysiological studies suggest
and teased nerve fibres studies usually confirm an
axonopathy. We were surprised to find a predomi-
nantly segmental demyelination in 2/5 patients who
had the same symptoms and the same course than the
others. In addition, mononuclear cell infiltrates seem
to be rare in muscle and nerve biopsies performed in
the DSPN of AIDS.11,17 Only 1/5 of our patients had
cell infiltrates in nerve biopsy but we noted that, in this
case, the HIV disease developed for only seven
months, which could explain the presence of immu-
opathogenic features. Inflammatory cell infiltrates
were also reported in this type of peripheral
neuropathy by Bailey et al.31 Prognosis of the DSPN of
AIDS is poor: 5/12 patients of our study and 18/26
patients reported by Cornblath et al8 died within six
months of the onset of the neuropathy. The cause of
this syndrome is subject to conjecture. Rance et al82
reported a selective gracile tract degeneration in all
four necropsy cases, and mild dorsal root ganglio-
neuritis in one case. These cases suggested a direct
retroviral infection of lumbosacral dorsal root gan-
glion cells with subsequent central-peripheral distal
axonal degeneration. However, De la Monte et al3
proposed that the axonopathy might be secondary to
T-cell and macrophage-mediated tissue destruction in the peripheral nerve. Further studies are necessary to know if these neuropathies are due to a direct retroviral action or to multiple causes (vitamin deficiency, side effects of drugs, opportunistic infections).

We thank Professors Castaigne, Laplane, Lyon-Caen and Chain for allowing us to study their patients, Dr Ratinahirana for performing the teased nerve fibres and Dr Dohin in his help in the follow up of the patients.

References

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