Subclinical peripheral nerve involvement in AIDS: an electrophysiological and pathological study

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Abstract

Thirty patients with AIDS without symptoms or signs of peripheral neuropathy were compared electrophysiologically with 23 age and sex matched healthy controls. The patients had a mean reduction in the amplitude of common peroneal compound muscle action potentials of 37% (95% CI 11-70%) and of sural sensory action potentials of 34% (CI 18-49%). Mean conduction velocity of both motor and sensory nerves was reduced by between 1 and 7 m/s, with a prolongation of F waves corrected for height of 5% in the arms and 13% in the legs. The distal motor latencies were unchanged. These changes did not correlate with the duration of AIDS, degree of immunosuppression (CD4 count), Body Mass Index, albumin or vitamin B12 level. Four patients had subclinical mononeuropathies. Sural nerve taken at necropsy from five asymptomatic AIDS patients had evidence of axonal degeneration without inflammation or demyelination. There was a mean reduction in myelinated fibre density of 30.5% (CI 10-51%) compared with eight age matched sudden death controls ($p = 0.01$). This loss principally affected the larger fibres. The pathological and electrophysiological changes indicate axonal degeneration and are similar to those seen in other chronic disorders and in normal ageing. It is concluded that this axonal degeneration is not specific to HIV.

A variety of peripheral nerve syndromes have been described during HIV infection.¹⁻⁶ In patients with AIDS a painful peripheral neuropathy and non-painful distal symmetrical peripheral neuropathy are the most commonly seen.^{1,4,6,7} In addition, electrophysiological⁸⁻¹⁰ and pathological^{11,12} reports have suggested that there may be subclinical peripheral nerve dysfunction.

A knowledge of the frequency, electrophysiological features and pathological substrate of the subclinical peripheral nerve involvement in AIDS is important in the assessment of symptomatic peripheral neuropathies in AIDS and of the neurotoxicology of drugs used in AIDS.^{13,14} We report the findings of a prospective electrophysiological and pathological study of peripheral nerves of asymptomatic patients with AIDS.

Materials

Patients

Asymptomatic AIDS Thirty male, homosexual or bisexual patients aged between 24 and 64 (mean 37) with AIDS,¹⁵ but without symptoms or signs of peripheral neuropathy were recruited, subject to their consent. The following were recorded: history of previous infections and the duration of AIDS,¹⁵ CD4 count, HIV antigen, Body Mass Index (weight/height²),¹⁶ serum albumin, and B12.

Patients were excluded from entry if they had been exposed to known neurotoxins (notably alcohol intake greater than 40 units per week, vincristine, isoniazid, thalidomide), or if they had a general medical condition, other than HIV infection, known to be associated with peripheral neuropathy (such as diabetes or uraemia), or a family history of peripheral neuropathy.

Patients were considered asymptomatic if on direct questioning they did not have any of the following symptoms, at any time persisting for greater than 24 hours and not related to definitively diagnosed focal central nervous system (CNS) disease: numbness, paraesthesiae, pain in the hands or feet, focal (distal or proximal) weakness. Patients who complained of generalised weakness and fatigue were included. Patients were examined and included if no neurological abnormalities were found or if the signs found could be unequivocally related to known focal CNS pathology.

The sural nerves were taken at necropsy from five patients with AIDS, who satisfied the exclusion criteria above, who had been examined between two and 20 days before death and in whom there were no symptoms or signs of peripheral nerve involvement. One patient (AIDS 2) had nerve conduction studies one month before death and is included in the electrophysiological study. The postmortem interval is given in table 2.

Controls

Electrophysiological Standardised electrophysiological studies were performed in 23 male volunteers aged between 21 and 45 (mean 31) recruited from hospital staff. The following exclusion criteria were used: homosexuality, any general medical condition associated with neuropathy, family history of neuropathy and symptomatic neuropathy.

Pathological sudden death controls (SDC) The sural nerve from four men and four women aged between 21 and 58 (mean 42) who had died suddenly were used as controls. The postmortem delay was between one and 22.5 hours, median nine hours. None of these

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patients had any factor known to predispose to peripheral neuropathy and none had known exposure to HIV. Six of them were included in a previous series of normal peripheral nerves.¹⁷ The two others died from subarachnoid haemorrhage and pituitary tumour.

Methods

Electrophysiology A Dantec 2000M EMG machine and surface electrodes were used (Stimulation: Medelec DPNSP 53054 and E/DS-K 53052 (ulnar and median sensory only); recording: Medelec MI 587 and (ulnar motor only) Dantec 12L20). The skin temperature of the limb examined was maintained at between 32 and 34°C by radiant heat. Stimulation frequency was 1 Hz and duration was 200 μ s. Filters were set with an upper frequency at 2 kHz and the lower at 20 Hz. The following were measured using the electrode placement described by Ma and Liveson¹⁸ and supramaximal stimulation: orthodromic median (index finger to wrist), ulnar (little finger to wrist) and antidromic sural (calf to ankle) sensory nerve action potentials; median (wrist to antecubital fossa) and superficial peroneal mixed nerve action potential and median, ulnar (both at wrist and elbow) and common peroneal (ankle and knee) motor conduction. Posterior tibial nerve motor conduction was performed if the latter was abnormal. The amplitude of a sensory nerve action potential was measured peak to peak from single potentials if clearly seen and reproducible. Potentials less than 5 μ V were averaged over 16 to 32 runs. A response was said to be absent if not obtained with at least two averaging runs of 32. The maximal conduction velocity for sensory and mixed nerves were calculated from the latency to onset. For motor conduction distal motor latency, peak to peak amplitude of compound muscle action potential and maximal motor conduction velocity, were measured.

The shortest latency of F waves evoked by 20 stimulation and recorded with surface electrodes over the abductor digiti minimi and the extensor digitorum brevis was noted. These were corrected using the following formula adapted from Kimura¹⁹: corrected F wave = height/(F wave latency – motor latency – 1). The result of this calculation therefore has the dimensions of a velocity and allows comparisons between patients and controls.

Pathology The sural nerve was taken at the ankle at the level of the lateral malleolus. A minimum length of 2 cm was fixed in 3% glutaraldehyde in 0.05 M Na cacodylate buffer, postfixed in 1% osmium tetroxide and processed to Araldite. The proximal 1 cm was stored in unpolymerised Araldite for teasing. Transverse sections at 1 μ m and ultrathin sections were taken. The processing and morphometric methods have been described in detail elsewhere.¹⁷ The following morphometric parameters were measured: myelinated fibre and unmyelinated axon densities; myelinated fibre and axonal diameters; unmyelinated axonal areas. Lamellae counts were performed on three SDC and one AIDS nerve using

unselected electromicrographs taken at between eight and 10 000 times and examined under a dissecting microscope. The areas of axons from the minimum of 60 fibres counted were measured using a Kontron MOP bit board. The cumulative relative frequencies were plotted.

Statistics Normally distributed data were analysed using the Student's *t* test. The Mann-Whitney-U test was used for non parametric analysis. Non parametric correlations were done using Spearman's rank correlation coefficient. The two sample Kalmogorov-Smirnov test was used to compare the cumulative frequencies of the lamellae counts and axonal areas. Confidence intervals (CI) for group mean reductions in electrophysiological and pathological parameters, when given, are at the 95% level.

Results

AIDS patients

The mean age of the asymptomatic AIDS patients and of the normal controls was similar. The duration of AIDS ranged from one to 40 months with a median of 11.5. These patients had a range of AIDS defining illnesses, many with more than one: *Pneumocystis carinii* pneumonia (PCP), 21 (70%), Kaposi's sarcoma, eight (27%), visceral candidiasis, seven (23%), cytomegalovirus (CMV) retinitis, seven (23%), CMV of gastrointestinal tract, six (20%), toxoplasmosis, four (13%), cryptosporidiosis, five (17%), and one of each of the following: lymphoma, cryptococcal meningitis, CMV pneumonitis and *Mycobacterium avium* intracellulare. The frequency of other related infections was herpes simplex, 14 (47%), H zoster, four (13%) and syphilis, 10 (33%). All patients had severe impairment of cell mediated immunity with CD4 counts between four and 482/ μ l though in all but two they were less than 100 (normal range 800–1200/ μ l). The median was 20.5/ μ l with an interquartile range of 10 to 67.5/ μ l.

There was evidence of weight loss; the weight height index ranged between 14.3 and 23 kg/m² with a mean of 19.9 kg/m² and interquartile range of 18.7 and 21.4 kg/m² (normal²⁰: mean 25.18, range 21.33–29.03 kg/m²). The albumin was low with a range of 23 to 44 g/l, mean 34 g/l, laboratory range 35–45 g/l. The serum B12 was below the lower limit of the normal range in five of the 21 patients where it was measured.

Electrophysiology

The results of the nerve conduction studies for both asymptomatic AIDS and controls appear in table 1, with the distributions of important parameters in fig 1. Differences were found both in sensory and motor conduction. There was a mean slowing of between 3–7 m/s (2–12%) in both arms and legs (table 1). The corrected F waves are also slower by a similar degree (5% in the arm, and 13.4% in the leg). Reduction in amplitude in both sensory and motor action potentials was more marked in the legs. In the

Table 1 A comparison of electrophysiological parameters between asymptomatic AIDS patients and normal controls. The means of each group and standard deviation (in brackets) are given. The percentage difference is the decrease from the negative controls. The significance (Mann-Whitney U) is given: * = $p < 0.01$; ** = $p < 0.001$; NS = not significant

	AIDS	Controls	% Difference	p
Sensory nerve action potentials (μ V):				
Ulnar	12.0 (4.2)	15.4 (6.0)	22	NS
Median	17.5 (6.6)	22.1 (8.4)	21	*
Sural	9.9 (3.5)	15.0 (4.5)	34	**
Sensory nerve maximum conduction velocity (m/s):				
Ulnar	52.0 (7.2)	58.8 (6.4)	11.6	**
Median	54.1 (7.2)	58.1 (6.5)	9.9	*
Sural	45.5 (7.5)	49.5 (5.6)	8.1	*
Mixed nerve action potentials (μ V):				
Median	22.9 (8.9)	29.7 (13.1)	23	**
S Peroneal	13.5 (7)	16.3 (6.4)	17	NS
Mixed nerve maximum conduction velocity (m/s):				
Median	52.9 (5.0)	57.0 (4.1)	7.2	**
S Peroneal	48.4 (9.3)	49.4 (6.8)	2.0	NS
Compound muscle action potentials (mV):				
Ulnar	10.5 (2.6)	14.4 (2.8)	27	**
C Peroneal	3.7 (2.0)	5.7 (2.8)	37	*
Maximum motor conduction velocity (m/s):				
Ulnar	57.3 (4.9)	60.2 (4.7)	4.6	*
Median	52.9 (5.0)	57.0 (4.1)	7.2	*
C Peroneal	43.9 (5.0)	49.8 (4.8)	11.8	**
Distal motor latency (ms):				
Ulnar	2.8 (0.7)	2.7 (0.4)	3.6	NS
C Peroneal	4.6 (0.7)	4.5 (0.8)	2.2	NS
F waves (corrected) (m/s):				
ADB	70.2 (5.5)	73.9 (4.9)	5.0	*
EDB	36.6 (3.9)	42.3 (3.8)	13.4	**

arms the reduction was between 22 and 29%, while in the legs it was 17% for the superficial peroneal mixed nerve action potential, 34% (CI 18–49%) for the sural sensory nerve action potential and 37% (CI 11–70%) for the common peroneal compound muscle action potential. There was no significant difference in the distal motor latencies.

These reductions did not correlate with either the nutritional status of the patient, the serum B12, the duration of AIDS or the degree of immune suppression as measured by the CD4. No differences in electrophysiological tests were found when comparing patients with abnormal serum B12 levels with the others. When patients were subdivided according to previous infections no significant associations were found though the number in each subgroup was small.

The common peroneal compound muscle action potential was below 1 mV in three

patients (10%) associated with relatively prolonged distal motor latencies. In all three the posterior tibial nerve on the same side had normal compound muscle action potential suggesting subclinical common peroneal palsies. In one patient there was a low ulnar compound muscle action potential (5 mV) with a 36% reduction across the elbow (5 mV distally, 3.2 mV proximally). This was interpreted as a subclinical ulnar neuropathy. The results from these nerves, thought to indicate isolated mononeuropathies, were not included in the group analysis, though the other studies in these patients were analysed.

Pathology

Preservation The preservation was good in all nerves taken at less than 12 hours and there were no discernible artefacts. Beyond this interval there were consistent artefacts that became increasingly marked with greater post-mortem delay. The earliest abnormalities, noted on electron microscopy, consisted of disorganisation of mitochondria and swelling of the Schwann cell cytoplasm, particularly in relation to the unmyelinated axons.¹⁷ In nerves with over 24 hours postmortem delay abnormalities in the myelinated fibres became apparent both on light and electron microscopy. Initially separation of the lamellae was noted, often associated with some separation of the axolemma from the inner aspect of the myelin sheath. Later these changes became more advanced and a frothy bubble like appearance was noted. Other changes included disorganisation of nuclear components, and, on teased fibres, more marked irregularities of myelin. Nerves with over 24 hour postmortem delay have not been used for the more detailed morphometry.

Sudden death controls (SDC) No inflammation was seen in any of these nerves. The perineurium and endoneurial collagen were normal.

Teased fibre preparations were normal, though in three nerves a very occasional degenerating fibre, as evidenced by myelin beading, was seen, particularly in the older patients. On electron microscopy occasional bands of Büngner were seen and there were very occasional regeneration clusters.

The morphometric findings are summarised

Figure 1 Scattergrams showing the distribution, in asymptomatic AIDS patients (closed circles) and in normal controls (open circles), of sensory action potentials of median (M) and sural (S) nerves; compound muscle action potentials of ulnar (U) and common peroneal (CP) nerves; and motor conduction velocities for ulnar (U) and common peroneal (CP). The horizontal line is the mean.

Table 2 Morphometric findings in asymptomatic AIDS and sudden death controls

No	Myelinated fibre density (per mm ²)	Density fibres > 7 µm	Unmyelinated axon density (per mm ²)	PM delay (hours)
SDC 1	9560	3728	35700	1
SDC 2	7460	2335	36400	17
SDC 3	8370	2164	31900	18
SDC 4	10190		41600	22.5
SDC 5	7760			8.5
SDC 6	6151	2227	26586	10
SDC 7	5815	2309	24460	6.5
SDC 8	7455	3429	19686	9.5
Mean	7845*	2699	30904	
AIDS 1	6333	1875	25788	3
AIDS 2	5699	1356	22204	20
AIDS 3	5261		20303	36
AIDS 4	5578		19772	48
AIDS 5	4400			48
Mean	5454*		22016	

*Significantly different ($p < 0.01$).

in table 2. The fibre diameter distribution from five of the seven have been combined in fig 2. The mean unmyelinated axonal area was $1.07\mu^2$ (range $0.87-1.38$).

Asymptomatic AIDS patients No inflammation was seen in any of these nerves. A Renault body was seen in one. No abnormalities were seen in the perineurium. The endoneurial collagen was normal. Degenerating fibres were identifiable in all nerves occasionally, on both teased fibres and in transverse sections (fig 3). These were usually limited to one per fascicle on transverse sections, except in case AIDS 5 when up to three per large fascicle were seen. The teased fibres showed very occasional paranodal demyelination and were otherwise normal. Bands of Büngner were seen more frequently than in the SDC. The morphometric analysis appears in table 2 and fig 2. The mean unmyelinated axonal area was $1.23\mu^2$ (range $1.21-1.26$).

On electron microscopy tubuloreticular structures were seen in the endothelial cells of endoneurial and epineurial blood vessels in all nerves examined. This finding has been discussed elsewhere.²¹

Degenerating fibres were found more frequently in the AIDS nerves than in the sudden death control. The myelinated fibre density was significantly lower in the AIDS nerves than in the sudden death controls. The mean was reduced by 30.5% (CI 10–51%) in the AIDS patients (fig 3). The nerve with the lowest myelinated fibre density was case AIDS 5, the nerve with the most marked degeneration. This reduction was not attributable to loss of axon diameter related to axonal atrophy as no

difference between the AIDS and the SDC nerves were found in the distribution of lamellae counts or axonal areas. The mean unmyelinated count was 28% lower in the AIDS nerves than in the sudden death controls, though this difference was not statistically significant. The unmyelinated axon densities fell within the lower end of the range defined by the sudden death controls. The morphological features of these unmyelinated axons did not differ between the two groups.

Discussion

The results obtained in the electrophysiological normal controls were similar to the normal ranges published by others using similar techniques.^{19,22} The morphometric data from the sudden death controls has largely been published before¹⁷ and is similar to other series of normal sural nerve from this age range.²³ Half the SDC nerves were from females while all the AIDS controls were male. No sex differences, however, have been reported in peripheral nerve morphology or morphometry. Both the normal electrophysiological controls and the sudden death controls were assumed to be HIV negative as all fell outside recognised at-risk groups.

The duration of AIDS, severity of immunosuppression (as measured by the CD4 count²⁴), spectrum and incidence of previous AIDS defining illnesses were similar to previously published clinical series.^{7,25,26} Notably, the rate of CMV infection is similar to our previously published control group of sequential AIDS admissions.⁷ Thus the population of asymptomatic AIDS patients in this study is representative of patients with AIDS admitted to hospital.

The reduction in amplitude and mild reduction in conduction velocities with preserved distal motor latency in the AIDS patients suggest that the principal change was axonal rather than demyelination. The decrease of sensory and motor nerve action potentials, and the less marked changes in velocity, were not associated with an increase in the standard deviation of these parameters. This suggests that this is due to an effect throughout the population of asymptomatic AIDS patients, rather than only within a subgroup who have developed subclinical neuropathies. Deterioration in function was found in 14 of 19 electrophysiological comparisons, when significance

Figure 2 Plot of the myelinated fibre density (per mm²) classified by fibre diameter of asymptomatic AIDS patients (broken line) compared with the mean of the sudden death controls (solid line) with 95% confidence intervals for that mean. AIDS 1 is shown on the left and AIDS 2 on the right.

Figure 3 Transverse sections of sural nerve from an asymptomatic AIDS patient (AIDS 1) on the left and a sudden death control (SDC 1) on the right. Degenerating fibres are marked with an arrow. Methylene Blue Azure II Basic Fuchsin, Bar 50 μ m.

was taken at the 5% level, as against one in 19 expected by chance, suggesting a small type I error. It will be noted that the percentage reduction is generally greater in the legs than in the arms. Although the level of significance attained is higher for the median and ulnar compared with the superficial and common peroneal nerves, the relevance of these differences in significance is questionable as these are dependent on the distribution of each variable.

The pathological findings in the sural nerves of AIDS patients also indicate axonal loss with a significant reduction in fibre density associated with low grade axonal degeneration and without inflammation. The larger fibres were reduced more than the smaller ones. The demyelination seen in the teased fibres would be compatible with secondary demyelination.

The electrophysiological and pathological data suggest that there is a low grade axonal loss in AIDS patients without symptoms of peripheral nerve dysfunction. The lower axonal density explains the reduction in sensory and motor evoked responses while the slight reduction in velocities may be attributed to this or to the preferential loss of larger fibres.²⁷ The findings are more prominent in the longest axons, and are consistent with either an axonopathy or a neuronopathy.

Electrophysiological changes have been described by others in HIV infection. So *et al*²⁸ report a similar reduction in conduction velocities and compound muscle action potentials in AIDS patients without clinical evidence of peripheral neuropathy. However, their

median nerve and the sural nerve sensory action potentials were closer to their normal range. In a serial study of HIV positive patients⁹ a 5% increase in latency in peripheral somatosensory evoked potentials developed over two years before the development of AIDS. It is difficult to compare other studies^{8 10 29 30} as these are either briefly reported, do not give the patient source, or classify results as normal or abnormal without giving raw data.

The reports of peripheral nerve pathology from asymptomatic AIDS patients are few. In a study of 21 postmortem nerves using only paraffin histology,¹¹ nine were described as having no peripheral nerve syndrome, though the method of clinical evaluation was not given and was presumably retrospective. There were signs of axonal degeneration in six, demyelination in nine and inflammation in seven. Another study, which used plastic embedded sections,¹⁸ examined sural nerves from 25 serial necropsies. They found 52% were normal, including fibre densities, though these values were not given. In the remainder there was a loss in fibre density, more marked for the larger myelinated fibres, but the lack of clinical correlation makes interpretation difficult. The detailed study by Gastaut *et al*¹⁰ is also difficult to interpret as results from both symptomatic and asymptomatic patients and from patients at all stages of HIV infection are combined.

Patients with AIDS differ from the control groups used in this study. Firstly, they are all homosexual or bisexual and often have had a number of sexually transmitted diseases such

as herpes simplex or syphilis. Secondly, they are all infected by HIV and have been for some years. Thirdly, all are immunocompromised and have had one or more opportunistic infection or tumour. Fourthly, they have been exposed to a variety of drugs, often for prolonged periods, for example cotrimoxazole for PCP prophylaxis. Lastly, they have often marked weight loss as indicated by the weight/height ratio, and may be malnourished and vitamin deficient.³¹

Which of these factors, or combination of these factors, lead to the subclinical peripheral nerve involvement found is not clear. Toxic or metabolic factors, weight loss, possible neurotoxic effects of drugs or infectious agents have been proposed as factors responsible for the distal sensory neuropathies seen in AIDS.^{14 28}

In our study, however, the duration of AIDS, degree of immunosuppression (CD4 count), Body Mass Index, B12 or albumen levels did not correlate with the electrophysiological abnormalities. Further, neither weight loss nor immunosuppression are essential factors for the latter as some changes occur early in HIV infection,⁹ before weight loss or immunodeficiency have developed and before any long term therapy has started.

Specificity of the axonal loss

Is the axonal loss observed specific to AIDS? Peripheral nerve abnormalities similar to those reported here have been described in patients with a variety of chronic diseases without clinical evidence of peripheral nerve involvement. Patients with lymphoma²² had a reduction, compared with normal controls, in median and common peroneal motor velocities of 13 and 11% and a reduction of median and ulnar sensory nerve action potentials and ulnar and common peroneal mixed nerve action potentials of about 50%. In sural nerves, axonal degeneration was seen with an overall reduction in myelinated fibre density of 21% but with no alteration in unmyelinated axon density. In patients with lung cancer³² motor conduction velocities were similar to our asymptomatic AIDS patients, with a reduction in median sensory action potentials. Twenty six per cent of patients with a variety of tumours had abnormal nerve conduction studies.³³ Patients with oat cell lung cancer³⁴ were found to have a peripheral neuropathy once 11% of body weight was lost, but not early in the disease, before losing any weight. However, electrophysiological findings were only reported for the common peroneal nerve and mononeuropathies of this nerve have been associated with voluntary weight loss of over 15%.³⁵ In chronic respiratory insufficiency sensory nerve action potentials were reduced by 17–34% and compound muscle action potentials by 33–46%, with normal conduction velocities.³⁶ In 50% of patients in intensive care there was mild slowing of conduction and a more marked reduction in sensory and motor evoked responses.³⁷ The more severe abnormalities in this latter group have been termed the "Critical illness polyneuropathy"^{38 39} and

are associated with axonal loss and degeneration.

A similar, but less marked, axonal loss is seen in association with normal ageing. There is a reduction in the conduction velocity of between eight and 12% in patients over 51 compared to those below 35 years,⁴⁰ and a reduction of between 11 and 18% in mean motor and sensory nerve action potentials in patients over 41 years compared with those under 40. These changes are associated with reduction in mean fibre density and evidence of mild axonal atrophy.¹⁷

The varying degrees of axonal degeneration and loss, with the consequent electrophysiological changes, seen also in a variety of chronic diseases and in ageing suggest that the phenomena are not specific to HIV infection and all might be considered as an "axonal loss of chronic disorders". It is therefore unlikely that HIV plays a direct role in their pathogenesis. The shared peripheral nerve findings may arise from a common response to a variety of insults specific to each disease or from a factor common to all.

The data presented here indicate that caution is required when using electrophysiological studies to evaluate peripheral nerve symptoms in patients with AIDS. They can be used as a guide in the assessment of such patients and as a baseline when evaluating potentially neurotoxic drugs.

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