Symptomatic polyneuropathy in human immunodeficiency virus antibody seropositive men with and without immune deficiency: a comparative electrophysiological study

Torben Smith, Johannes Jakobsen, Johannes Gaub, Werner Trojaborg

Abstract

Symptomatic polyneuropathy in human immunodeficiency virus (HIV) infection was studied in ten men with acquired immunodeficiency syndrome (AIDS) and in ten men without the immune deficiency. In both groups of patients electrophysiological signs of polyneuropathy of the axonal type were present in the sural, median and peroneal nerves. The AIDS patients had a greater reduction of the mean (SD) sural nerve action potential, 3.1 (2.7) μ V, than in patients without AIDS, 10.2 (6.1) μ V ($p < 0.01$) and greater slowing of peroneal nerve conduction velocity, 42.6 (1.4) m/s in AIDS patients versus 52.6 (3.3) m/s in patients without AIDS ($p < 0.0001$). These findings indicate that in most HIV infected patients the severity but not the type of neuropathy depends on whether an immune deficient state has developed. Seven patients with symptomatic polyneuropathy were treated with azidothymidine (AZT) for an average of 10 months and compared with a group of five untreated patients with similar symptoms. No effect of AZT treatment on sural or median nerve amplitude or conduction velocity or on the vibratory or temperature thresholds was observed.

Human immunodeficiency virus (HIV) infection is associated with several forms of peripheral neuropathy including distal symmetrical polyneuropathy, inflammatory demyelinating polyneuropathy and mononeuropathies.¹⁻¹⁰ The distal symmetrical polyneuropathy occurs in a large proportion of acquired immunodeficiency syndrome (AIDS) patients and is characterised by mild slowing of conduction velocity, amplitude reduction of the action potential and fibre loss. In contrast, chronic or acute inflammatory demyelinating polyneuropathy can be the presenting symptom of HIV infection and are held to be the predominant form of symptomatic polyneuropathy in HIV infected subjects without AIDS. This condition is characterised by considerable slowing of the conduction velocity, conduction block and pathologically by inflammatory infiltrates and demyelination.

To examine whether the predominant

forms of symptomatic polyneuropathy in HIV seropositive patients with and without AIDS are different a clinical and electrophysiological study was carried out on two groups of ten patients each. In addition, we report the results of a small and prospective study on the effect of azidothymidine (AZT) treatment in seven of the twenty patients studied.

Patients and methods

Patients

Ten homosexual men with AIDS and ten HIV seropositive homosexual immune competent men, who were referred to the department of clinical neurophysiology for diagnosis of symptoms compatible with polyneuropathy were included in the study. Informed consent was obtained from the two groups. The presence of HIV antibody was confirmed by Western Blot analysis. The time of seroconversion was unknown. In seven of these patients (two had AIDS, five were HIV-seropositive without AIDS) treatment with AZT (1000-1200 mg each day) was started and a follow up study was carried out after a treatment period of 10 (3) months. Five of the untreated patients were used as controls. No toxic or metabolic causes of the neuropathy were found and there was no family history of neuromuscular disorders. At the clinical examination special attention was paid to symptoms commonly associated with peripheral neuropathy.

The vibratory perception threshold was determined on the pulp of the thumb and on the pulp of the big toe. The vibratory stimulus was harmonic mechanical oscillations of 100 Hz, delivered by an electromagnetically driven vibrator (Biothesiometer, Biomedical Instruments, Newbury, Ohio). The values were compared with normal subjects matched for age and sex.¹¹

Cutaneous thermal thresholds of the foot were tested using a portable computer system.¹² A sequence of dynamic thermal test stimuli (cold or warm) of varying intensities was applied to the patient's skin (sole of the foot) using a thermoelectric module which effected a temperature change according to the Peltier principle. The polarity of the current could be set so that the device either heated or cooled the skin, and thresholds for each were measured separately and compared with values from normal subjects matched for age.

Departments of
Clinical
Neurophysiology,
Neurology and
Infectious Diseases,
Rigshospitalet,
University of
Copenhagen,
Copenhagen,
Denmark
T Smith
J Jakobsen
J Gaub
W Trojaborg

Correspondence to:
Dr T Smith, Department of
Clinical Neurophysiology
145, Hvidovre Hospital,
Kettegaard Alle 30, DK-
2650 Hvidovre, Denmark.

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Table 1 Clinical and electrophysiological features of 10 HIV-seropositive patients without AIDS and 10 patients with AIDS

	HIV-seropositive patients without AIDS	AIDS patients	Normal controls
	Mean (SD)		
Age (years)	40 (7.7)	41 (8.6)	
Recognised duration of HIV/AIDS (months)	20 (10.9)	12 (7.1)	
Duration of symptoms (months)	12 (12.7)	8 (10.3)	
Vibratory perception threshold (V)			
thumb	4.1 (0.6)	5.1 (0.8)	5.0 (0.8)
big toe	11.5 (7.3)	16.9 (5.8)*	10.0 (3.0)
Sural nerve			
CV (m/sec)	45.6 (3.5)*	42.7 (4.4)*	53.1 (2.4)
Amplitude (μ V)	10.2 (6.1)*	3.1 (2.7)**	29.6 (4.7)
Median nerve, motor			
CV (m/sec)	59.0 (3.0)*	55.1 (3.6)*	63.0 (4.5)
Peroneal nerve, motor			
CV (m/sec)	52.6 (3.3)	42.6 (1.4)**	51.0 (4.7)

*HIV-group and AIDS-group compared to controls, $p < 0.05$.**AIDS-group compared to HIV-group, $p < 0.01$.

Electrophysiological studies

The conduction velocity of the sural nerve was determined according to the method of near-nerve recording.¹³ In short, sensory fibres of the sural nerve were stimulated by needle electrodes at the lateral malleolus and

the evoked sensory action potential (SAP) was recorded via needle electrodes 12–15 cm proximal to the malleolus. The recording electrode was adjusted near the nerve until the largest sensory potential was obtained. When the SAP was less than 2 μ V electronic averaging of up to 1000 responses was used to identify a sensory potential. Motor conduction studies were performed on the median and peroneal nerves in the forearm segment and in the segment from knee to ankle, respectively, stimulating and recording with surface electrodes. To maintain a constant temperature of 34–36°C the arm and leg were heated by an infra-red heating element which was controlled by a thermo-couple on the skin. Findings in sensory and motor nerves in patients were compared with those in normal subjects matched for age.¹⁴

STATISTICS

Electrophysiological differences between patients with and without AIDS were tested by the unpaired t test using a 0.0125 limit of significance (Bonferroni correction). T test comparisons between patient and control groups as well as between treated and untreated groups were performed using a 0.05 limit of significance.

Results

The clinical features of the two groups of patients are summarised in Table 1. Age was similar in the two groups and there was no significant difference between duration of symptoms. All patients had symptoms of lower extremity sensory disturbances, paraesthesia or hypoaesthesia, suggesting a distal symmetrical polyneuropathy. Three of the HIV seropositive patients without AIDS and four of the AIDS patients had painful feet. Only three patients had motor symptoms (one HIV seropositive and two with AIDS). The clinical signs of neuropathy were generally mild, were more frequently observed in the AIDS patients, and affected mainly the lower extremities. No evidence of chronic inflammatory neuropathy was found. The vibratory perception threshold of the big toe was sig-

Figure 1 Sensory conduction velocity along the sural nerve from the lateral malleolus to mid-calf in 10 HIV seropositive patients without AIDS (open circles) and in 10 patients with AIDS (dots). The solid line indicates the normal mean, the thin lines indicate the 95% upper and lower confidence limits.

Figure 2 Amplitude of the sural nerve action potential. Symbols and lines as in fig 1. Ordinate, amplitude in μ V, logarithmic scale.

Table 2 Sensory and motor conduction studies, vibratory and thermal thresholds in 12 HIV-seropositive patients followed for six to 15 months

	AZT-treatment		Controls	
	First examination	Second examination	First examination	Second examination
Sural nerve				
CV (ms)	44.9 (3.8)*	44.9 (4.4)	49.6 (3.4)	47.6 (2.6)
Amplitude (μ V)	7.2 (4.8)	11.6 (8.4)	20.0 (10.2)	17.8 (6.1)
Median nerve				
CV (ms)	61.7 (5.0)	61.0 (8.5)	56.3 (2.5)	54.3 (2.9)
Amplitude (mV)	13.0 (7.9)	11.0 (2.7)	14.8 (3.3)	14.8 (3.7)
Vibratory threshold				
Thumb (V)	3.6 (0.5)	4.0 (0.7)	4.3 (0.5)	4.8 (1.0)
Big Toe (V)	12.8 (9.0)	9.8 (7.7)	6.8 (2.8)	6.3 (1.3)
Temperature threshold				
Cooling ($^{\circ}$ C)	0.8 (0.4)	1.3 (1.2)	0.8 (0.6)	0.9 (0.4)
Warming ($^{\circ}$ C)	2.1 (2.5)	2.5 (2.2)	2.1 (2.5)	2.1 (2.5)

*Values are mean (SD).

nificantly increased in patients with AIDS only.

Table 1 summarises the electrophysiological findings: conduction velocities of the median and sural nerve were slightly reduced in both groups of patients (fig 1). In the peroneal nerve AIDS patients only had slowing of conduction. The amplitude of the sural nerve action potential was considerably reduced in both groups of patients (fig 2).

HIV seropositive men without AIDS had better preservation of all four electrophysiological parameters than those who had developed the immune deficiency. However, only the reduction of the sural nerve action potential and the peroneal nerve conduction velocity were significantly better preserved in immune competent men.

The mean (SD) time between the first and the second examination was 10 (3) months, range 6–15 months. Most patients had symptoms for more than a year. The clinical stage of HIV infection¹⁵ remained unchanged in all patients. No significant clinical or immunological differences were observed between the first and the second examination except that a few patients in both groups had lost their deep tendon reflexes. Table 2 shows that no significant changes of sensory or motor nerve conduction velocity, amplitude or vibratory and temperature threshold occurred in the groups during the follow up period.

Discussion

In this study none of the ten HIV seropositive immune competent men with symptomatic polyneuropathy showed electrophysiological signs of demyelination characterised by profound slowing of the conduction velocity. Contrary to expectations immune competent patients had less slowing of conduction velocity than patients who had developed AIDS.

In both groups of patients the electrophysiological findings are compatible with an axonal polyneuropathy. We have previously shown that slight slowing of nerve conduction occurs in the majority of HIV seropositive immune competent subjects without symptoms of neuropathy and that the electrophysiological disturbances progress with

time.^{16 17} A possible explanation for the more severe electrophysiological impairment in the AIDS patients is that the duration of HIV infection in this group is longer. Our control group was a population with unknown sexual preferences. It is not known whether homosexual and heterosexual men have different peripheral nerve function. None of our patients used alcohol, medication or "recreational drugs" to a degree which can explain impairment of nerve function.

The electrophysiological results are most compatible with a distal axonal polyneuropathy affecting both sensory and motor fibres. Thus the degree of slowing in the sural, median and peroneal nerves in both groups of patients are well within the range expected from axonal degeneration of large myelinated fibres.^{18 19}

The vibratory perception threshold of the big toe was significantly elevated in the patients with AIDS indicating a length dependent affection of the large myelinated afferent nerve fibres.²⁰ We tested temperature thresholds in the HIV seropositive patients without AIDS and observed that the threshold for warming was very much elevated, mean (SD) was 3.7 (2.2) $^{\circ}$ C; in normal subjects the upper 95% confidence limit was 2.1 $^{\circ}$ C, which indicates that the neuropathy also affects small unmyelinated fibres (preliminary finding).

Our results agree with other reports of electrophysiological studies on AIDS patients with associated distal polyneuropathy,^{6–10} with features of a dying back axonal neuropathy. An association between the affected part of the peripheral nervous system (myelin, axon, root) and the stage of the HIV infection has been proposed in several reports.^{4 6 7} HIV seropositive patients without AIDS are said primarily to have inflammatory demyelinating peripheral neuropathies.^{3 4 21} In our study the clinical and electrophysiological evidence indicates that a distal symmetrical polyneuropathy also exists in HIV seropositive patients without AIDS.

It appears that every part of the nervous system is vulnerable to HIV infection. We have previously described clinical and electrophysiological evidence of myelopathy in patients with AIDS and in patients with HIV seropositivity but without AIDS.^{5 16 17} It is

therefore difficult to localise lesions in the nervous system of HIV infected patients, and it is advisable to include electrophysiological studies in the evaluation of these patients.

In anecdotal reports, AZT treatment of HIV patients with associated neuropathy have shown conflicting results. Patients with HIV induced dementia and neuropathy have shown clinical improvement after administration of AZT.²² Another study showed clinical and electrophysiological improvement in one patient after two months of AZT treatment.²³ In a third study three patients with predominantly sensory neuropathy were given AZT and none improved.⁷ No systematic trial of AZT has been published. In our group of HIV patients with neuropathy we did not observe any significant improvement of the clinical and electrophysiological measures during AZT treatment. No deterioration, however, took place in our control subjects during the follow up period indicating that our observation period might be too short.

The aetiology and pathogenesis of peripheral neuropathy associated with HIV infection is uncertain. HIV virus has been cultured from peripheral nerves^{24,25} and viral particles have been identified in a sural nerve biopsy⁸ suggesting direct viral infection of the nerve. A circulatory factor which attacks peripheral nerves, making them vulnerable to virus infection, could also play a role.⁶ Infection of peripheral nerves with HIV or opportunistic viruses such as cytomegalovirus is strongly suspected in patients with distal symmetrical polyneuropathy, but has never been demonstrated. Further studies of this condition as well as its response to treatment are needed.

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