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ORIGINAL COMMUNICATION

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Peripheral neuropathy in HTLV-I infected individuals without tropical spastic paraparesis/HTLV-I-associated myelopathy

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Abstract Tropical spastic paraparesis/HTLV-I-associated myelopathy (TSP/HAM) is the classical neurological manifestation of HTLV-I. Only a few studies have described isolated peripheral neuropathy (PN) among HTLV-I infected individuals. 335 infected individuals without TSP/HAM were evaluated for the presence of PN and 45 of them showed evidences of peripheral nervous system involvement. Of these 21 patients had isolated PN, defined by clinical and/or electrophysiological criteria. Sural nerve biopsies revealed inflammatory infiltrates in 2, axonal degeneration in 2 and segmental demyelination in 1. Therefore, peripheral neuropathy can be found as an isolated manifestation of HTLV-I infection. We conclude that HTLV-I infection should be investigated in patients with PN of unknown origin.

Key words HTLV-I · peripheral neuropathy · TSP/HAM

Introduction

The human T cell lymphotropic virus type 1 (HTLV-I) is the etiological agent of Tropical Spastic Paraparesis/HTLV-I Associated Myelopathy (TSP/HAM) [18] and Adult T cell Leukemia/Lymphoma (ATLL). Myopathy, dysautonomia, mild cognitive dysfunction, cerebellar syndromes, and peripheral neuropathy (PN) have also been described in infected individuals, usually in association with the myelopathic syndrome known as TSP/HAM [2, 5, 6, 15, 23]. There is controversy over whether TSP/HAM is the sole neurological manifestation of HTLV-I. Certainly it has been the most easily detectable neurological manifestation of HTLV-I but other less symptomatic disorders not restricted to the spinal cord might also be part of a wider HTLV-I-associated neurological complex [3, 19, 20, 23]. Isolated PN has not been systematically studied in HTLV-I infected individuals. Only a few cases of isolated PN without symptoms and signs of TSP/HAM have been reported so far [7, 16]. The present study aims to investigate and describe the characteristics of PN in HTLV-I infected individuals without TSP/HAM.

Patients and methods

The Reference Centers on Neurological Infections and HTLV, at the Evandro Chagas Clinical Research Institute – FIOCRUZ, Rio de Janeiro, Brazil, receives HTLV-infected individuals from blood banks, and from neurology, hematology and infections diseases services from other hospitals in Rio de Janeiro. Patients with Adult T Cell Lymphoma/Leukemia (ATL) are followed at the National Cancer Institute. Between May 1993 and September 2002, 514 HTLV-I infected individuals were admitted to our institution. HTLV-I infected individuals fulfilled international criteria for serological positivity at both ELISA *(Vironostika HTLV-I/II – Organon, Netherlands)* and Western Blot *(Genelabs Diagnostics 2.4, Singapore)* tests.

One hundred seventy nine patients fulfilled diagnostic criteria for

TSP/HAM [17]. To identify cases of isolated peripheral neuropathy in the remaining 335 infected individuals without TSP/HAM, inclusion and exclusion criteria were applied. Each patient underwent a full neurological examination and detailed electrophysiological studies according to a specific protocol and all of them gave their informed consent prior to their inclusion in the study. Nerve biopsies were performed only after formal consent. The exclusion criteria were concurrent infection with HIV, HTLV-II, syphilis, hepatitis B and/or C virus and conditions that could by themselves cause PN (such as hypothyroidism, vitamin B12 deficiency, chronic use of potentially neurotoxic drugs, diabetes, leprosy, alcoholism and hepatic, renal or genetic diseases). We also excluded individuals with isolated mononeuropathies such as carpal tunnel syndrome, since it is multifactorial and highly prevalent in the general population. The inclusion criteria were characteristic symptoms and/or signs of PN (hypoesthesia, burning sensations, paresthesia, hyperesthesia, weakness and diminished or abolished ankle reflexes) and/or abnormal electrophysiological tests. Electromyography and nerve conduction studies were done using the Neuropack Σ, 4 channel MEB 5504K *(Nihon Kohden Corporation, Tokyo, Japan)*. Our protocol included the following tests: motor conduction studies (distal motor latency, conduction velocity, amplitude, form and duration of the compound motor action potential) of median and peroneal nerves on one side, ulnar and tibial nerves on both sides; sensory conduction studies (distal sensory latency, amplitude and form of the sensory nerve action potential) of median, ulnar and radial nerves on one side and sural nerve on both sides; F waves studies (minimum F wave latency and F wave frequency) of ulnar and tibial nerves on both sides; and H reflex studies. Needle electromyography examination of at least one lower limb was performed as part of routine examination. Polyneuropathy was characterized by the symmetric involvement of two or more peripheral nerves and was further classified into sensory, motor, or mixed as well as into axonal or demyelinating. Multiple mononeuropathy was defined by the asymmetric involvement of two or more sensory, motor or mixed peripheral nerves. Biopsy specimens were processed for light microscopy, including semithin transverse sections. Finally, patients were classified into two groups: (1) Defined Peripheral Neuropathy, if there were symptoms and/or signs plus abnormal electrophysiological studies or nerve biopsy, and (2) Probable Peripheral Neuropathy, if there were symptoms and/or signs with normal electrophysiological studies.

Results

Forty-five out of 335 infected individuals without TSP/HAM (45/335; 13.4 %) had symptoms and/or signs of PN. Twenty-four out of these individuals were excluded; 9 owing to isolated mononeuropathy (carpal tunnel syndrome), 3 to insufficient follow up and 12 to the presence of other concurrent conditions. Therefore, 21 individuals (21/335; 6.2 %) were included in this study (11 males; mean age 45.6 years). Sexual transmission was the most probable route of infection in nine, blood transfusion in four, breast-feeding in three and in five it could not be determined. Eleven patients (52 %) had some neurological complaint and 17 (81 %) had an abnormal neurological examination. In 12 (57 %) there were some electrophysiological abnormalities (Table 1). Only five of the 21 patients included in the study agreed to be biopsied. All the five sural nerve specimens were abnormal (Fig. 1). In one patient (Patient #10) a muscle and nerve biopsy was performed, despite normal clinical examination and electrophysiological studies, because of a persistent elevation of creatine kinase and the presence of disabling paresthesia. An inflammatory infiltrate was disclosed (Fig. 1). Semithin transverse sections showed evidence of axonal degeneration in two cases (Fig. 2). Clinical, laboratory and demographic data are summarized in Table 1.

Discussion

In TSP/HAM the reported frequency of PN has varied from negligible to 32 % [4, 14, 21]. However, in HTLV-I infected individuals without TSP/HAM the prevalence of PN is at present unknown. The prevalence of PN in HTLV-I negative blood donors of Rio de Janeiro is around 2.5 % [12]. Although our study is a descriptive analysis, we observed an impressive number of PN in a

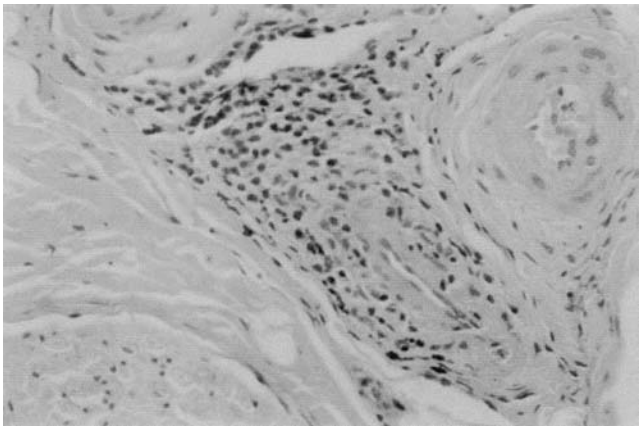

Fig. 1 Sural nerve biopsy from patient 10, revealing a dense inflammatory mononuclear cell infiltrate in the epineuria surrounding and infiltrating a blood vessel wall (H&E 40 x)

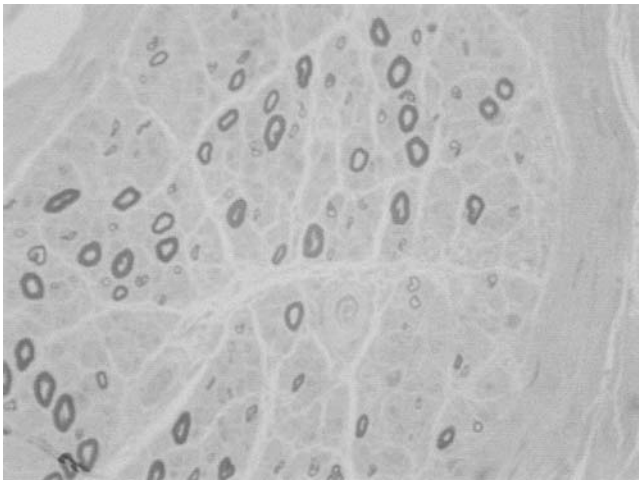

Fig. 2 Sural nerve biopsy from patient 4, showing loss of large and small myelinated fibers. Toluidin blue 40X

Table 1 Main characteristics of HTLV-I-associated peripheral neuropathy (HAP)

Patient	Age (years)	Sex	Knee Jerk	Ankle Jerk	Neurological complaints	Sensory Involvement	EMG/NCS	Type	Biopsy	Group
1	47	F	↓	↓	–	Hypoesthesia	SM PN	Mx	–	HAP
2	48	F	↓	∅	Paresthesias	Hypoesthesia	SM PN	Mx	PII	HAP
3	39	M	∅	∅	–	Dysesthesia	SM PN	Ax	–	HAP
4	39	M	Normal	Normal	–	Normal	SM PN	Mx	AD	HAP
5	39	M	∅	∅	–	Normal	SM PN	Ax	–	HAP
6	61	F	∅	∅	–	Normal	Normal	–	–	Probable HAP
7	40	M	↓	∅	–	Normal	M PN	Ax	–	HAP
8	41	M	Normal	↓	Paresthesias	Normal	M PN	Dm	–	HAP
9	54	F	Normal	↓	Paresthesias	Loss of vibration sense	Normal	–	–	Probable HAP
10	32	M	Normal	Normal	Paresthesias	Normal	Normal	–	PII	HAP
11	59	M	↓	∅	Paresthesias	Hypoesthesia	SM PN	Ax	AD	HAP
12	34	M	∅	∅	–	Loss of vibration sense	Normal	–	–	Probable HAP
13	53	F	∅	∅	Paresthesias	Normal	Normal	–	–	Probable HAP
14	46	F	Normal	↓	Paresthesias	Normal	Normal	–	SD	HAP
15	21	M	Normal	Normal	–	Normal	M PN	Dm	–	HAP
16	55	F	Normal	Normal	–	Normal	S PN	Ax	–	HAP
17	40	F	↓	∅	–	Normal	MM	Mx	–	Probable HAP
18	59	F	↓	↓	Paresthesias	Normal	Normal	–	–	Probable HAP
19	67	M	↓	∅	Autonomic Symptoms	Hypoesthesia	SM PN	Ax	–	HAP
20	52	M	Normal	↓	Paresthesias	Normal	Normal	–	–	Probable HAP
21	31	F	∅	∅	Autonomic Symptoms	Dysesthesia	Normal	–	–	Probable HAP

M Male; *F* Female; ↓ diminished; ∅ abolished; *EMG/NCS* Electromyography/Nerve conduction studies; *M PN* Motor Polyneuropathy; *SM PN* Sensorimotor polyneuropathy; *MM* Multiple mononeuropathy; *Dm* Demyelinating; *Ax* Axonal; *Mx* Mixed; *AD* Axonal Degeneration; *SD* Segmental Demyelination; *PII* Perivascular inflammatory infiltrate; *HAP HTLV-I* associated peripheral neuropathy

population of HTLV-I infected individuals without TSP/HAM or other concurrent conditions (21 out of 335 infected individuals; 6.3 %).

Since 1989 we have being following a large cohort of HTLV-I infected individuals with and without TSP/HAM. In this population the clinical interview frequently reveals complaints suggestive of PN. In the present series, isolated peripheral nerve involvement was characterized mostly by a polyneuropathy including distal features such as paresthesias, stocking-type peripheral sensory loss, absent ankle jerks and abnormal electrophysiological and sural nerve biopsy findings. These findings are consistent with a predominantly sensory polyneuropathy.

The pathogenesis of neurological disorders in HTLV-I infection is not fully understood, but there is evidence that the lesion may not be restricted to the spinal cord [3, 19, 20]. The prevalence of brain lesions in magnetic resonance imaging in TSP/HAM varies from 50 % to 80 % [8]. These white matter lesions are supposed to be caused by a chronic perivascular inflammation. Akizuki et al. demonstrated perivascular lymphocytic infiltration in the central nervous system, suggesting that vasculitis might be an important pathological feature of TSP/HAM [1]. This may explain the diffuse nature of such lesions, suggesting that TSP/HAM is in fact a chronic multifocal leukomyeloencephalopathy.

The pathogenesis of peripheral nerve involvement in HTLV-I infection is at present unknown. There has been no evidence of direct viral infection of the peripheral nervous system. In addition, previous studies demonstrated that spinal nerve roots are also involved in the inflammatory process that causes TSP/HAM [10]. Therefore, either a proximal or a distal inflammatory mechanism may be responsible for PN associated with TSP/HAM. Lymphocytic infiltrates have been observed in both spinal cord and muscle tissues in patients with HTLV-I-associated polymyositis [9]. Said et al. also de-

scribed perivascular inflammation in a patient with PN and TSP/HAM [22]. In another study, Bhigjee et al. observed varying degrees of axonal atrophy demyelination, remyelination, and perineural fibrosis in sural nerve biopsy specimens from six TSP/HAM patients with PN. However, they failed to demonstrate any inflammatory infiltrates in these specimens [5]. More recently, Kiwai et al. described nine biopsy-proven cases of PN in association with TSP/HAM [10]. Sural nerve pathology of these individuals revealed a combination of demyelination and remyelination, and axonal degeneration and regeneration. They also failed to demonstrate inflammatory infiltrates in these samples.

Only a few (~5%) infected individuals will develop TSP/HAM. The reason for that is unknown. It has been shown that TSP/HAM patients have a higher proviral load than asymptomatic carriers (AC) [13]. This can lead to a strong inflammatory response that is considered to be the basic mechanism of this myelopathy. However, subjects with other neurological diseases such as PN, myopathy or isolated neurological signs at the clinical examination [11, 12] have a proviral load as high as TSP/HAM patients when compared with AC (Andrada-Serpa MJ, personal communication). Therefore, if this finding is further confirmed, we could speculate that HTLV-I infected individuals with other neurological diseases could either represent a new subset of neurological manifestation of HTLV-I or an initial or subclinical form of TSP/HAM. Consequently, we believe that a broader spectrum of neurological disorders may be associated with HTLV-I, which may or may not include TSP/HAM.

Another interesting point that may support our present findings is the higher prevalence of PN in HIV-1/HTLV-II confection when compared with HIV-1 infected individuals [24]. Therefore, HTLV-II could be a predisposing cofactor for the development of PN among HIV-1-infected patients. The same could apply to HTLV-I infection given that HTLV-I shares similar structural and biological properties with HTLV-II.

In summary, we found that HTLV-I infected individuals can have a peripheral neuropathy in the absence of TSP/HAM, as demonstrated by clinical examination, electrophysiological studies, and sural nerve biopsy. Although isolated PN seems to be a less disabling aspect of the neurological spectrum of HTLV-I infection, this virus should be investigated in those cases of PN of unknown etiology in endemic areas. We believe that the confirmation of the present findings in a larger sample, coupled with systematic proviral load measurements could add isolated PN to the neurological spectrum of HTLV-I infection.

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