

THE FREQUENCY OF PERIPHERAL NEUROPATHY IN A GROUP OF HIV POSITIVE PATIENTS IN BRAZIL

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ABSTRACT - Peripheral neuropathy is a common neurological complication occurring in asymptomatic and symptomatic stages of HIV infection. The most common syndromes are distal symmetric polyneuropathy, inflammatory demyelinating polyneuropathy, polyradiculopathy, mononeuropathy, mononeuropathy multiplex and autonomic neuropathy. *Purpose:* To evaluate the frequency of peripheral neuropathy in a group of HIV seropositive outpatients in São Paulo, Brazil. *Method:* Over a period of 17 months, 49 HIV+ patients were evaluated clinically. Laboratory analysis and electroneuromyography were requested to all patients. *Results:* Thirty four (69.4%) of the 49 patients had the diagnosis of peripheral neuropathy established on clinical grounds. The most common sign was impairment (97.1%) of sensibility. Thirteen (33.3%) of the 39 that were subjected to electroneuromyography had features of peripheral neuropathy, being a sensitive-motor axonal neuropathy the most common. No abnormalities were found in the laboratory analysis performed in 42 patients, except in four who had VDRL positive. *Conclusion:* A peripheral neuropathy was frequently found upon clinical examination in our group of HIV positive individuals.

KEY WORDS: peripheral neuropathy, HIV, AIDS.

Frequência da neuropatia periférica no Brasil em um grupo de pacientes HIV positivo

RESUMO - A neuropatia periférica é complicação neurológica comum, podendo ocorrer nas fases assintomáticas e sintomáticas da infecção pelo vírus da imunodeficiência humana (HIV). As síndromes mais comuns são a polineuropatia distal simétrica, polineuropatia desmielinizante inflamatória, polirradiculopatia, mononeuropatia, mononeuropatia múltipla e neuropatia autonômica. *Objetivo:* Avaliar a frequência da neuropatia periférica em um grupo de pacientes HIV positivo em São Paulo, Brasil. *Método:* Em um período de 17 meses, foram avaliados clinicamente 49 pacientes HIV positivos. Foram solicitados exames laboratoriais e eletroneuromiografia (ENMG) para todos os pacientes. *Resultados:* Foi estabelecido o diagnóstico clínico de neuropatia periférica em 34 (69,4%) dos 49 pacientes. O sinal neurológico mais comum foi a alteração da sensibilidade (97,1%). Treze (33,3%) dos 39 pacientes que realizaram a ENMG tiveram o diagnóstico de neuropatia periférica, sendo a neuropatia sensitivo-motora axonal o achado mais comum. Não foram encontradas alterações significativas nos exames laboratoriais (42 pacientes realizaram os exames), com exceção de quatro pacientes em que o VDRL foi positivo. *Conclusão:* A neuropatia periférica foi um achado frequente no grupo de pacientes HIV positivo estudados clinicamente.

PALAVRAS-CHAVE: neuropatia periférica, HIV, SIDA.

The acquired immunodeficiency syndrome (AIDS) was first described in 1981. At that time it was reported the occurrence of an uncommon opportunistic infection caused by *Pneumocystis carinii* in a previously healthy young homosexual man¹. Neurological disorders in HIV patients were first reported in 1982². Peripheral neuropathy is a common neurological complication associated with human immunodeficiency virus type 1 (HIV-1) infection, occurring in asymptomatic and symptomatic individuals³⁻⁵ and it can be the first manifestation of the disease⁶. The peripheral neuropathy syndromes are somewhat specific according to the stage of the disease (Table

1). This specificity reflects the distinct mechanisms of the various types of peripheral neuropathies in HIV seropositive individuals⁶⁻¹¹.

The prevalence of peripheral neuropathy associated with HIV-1 is estimated at 15 to 50% of patients^{7,12-15}. But it may be almost 100% when a pathological study is performed^{14,15}. Distal symmetrical polyneuropathy (DSP) is the most common peripheral nerve involvement in HIV-positive individuals^{3,16}. There are other forms of peripheral neuropathies in HIV-positive patients including inflammatory demyelinating polyneuropathy^{6,17}; progressive polyradiculopathy^{6,9}; mononeuropathy and mononeuropathy multiplex^{10,18}; autonomic neuropathy⁸;

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and diffuse infiltrative lymphocytosis syndrome¹⁹ (Table 1).

The objective of this study was to evaluate the frequency of peripheral neuropathy in a group of HIV-seropositive out-patients in São Paulo, Brazil.

METHOD

Over a period of 17 months, from July 1999 to May 2000, 49 HIV-positive patients were evaluated at the AIDS Outpatient Clinic of the Infectious Diseases Division of the UNIFESP - Escola Paulista de Medicina in São Paulo, Brazil.

Each patient arbitrarily recruited by the Coordinating Nurse had a history taken and neurological examination done by the same neurologist, mostly looking for the diagnosis of a peripheral neuropathy. Although highly suspicious of a peripheral neuropathy, symptoms of extremity pain, numbness, tingling and weakness were not enough to make the diagnosis. The diagnosis was established when we found any of the following, isolated or combined: sensory impairment, absent deep tendon reflexes, amyotrophy and weakness. We examined thermal, tactile, pain, vibration and position sense sensory modalities. Weakness was considered diagnostic if it had a pattern compatible with any form of peripheral neuropathy²⁰. Laboratory analysis (glucose, CBC, BUN, creatinine, electrolytes, liver function, vitamin B12, VDRL, HTLV 1/2) and electroneuromyography²¹ were requested to all patients.

The present study was approved by the ethics committee of the UNIFESP - Escola Paulista de Medicina. Informed consent was obtained from all patients.

RESULTS

Of the 49 patients included, 32 were male and 17 female. The mean age was 36.88 years with a range of 21-53 years. None of the patients had history of familial peripheral neuropathy, diabetes mellitus or recent (less than 2 years) history of alcohol abuse. Thirty four of our 49 patients (69.4%) had diagnosis of a peripheral neuropathy. Twelve (35.3%) had both symptoms and signs and 22 had only signs. Decreased distal superficial sensibility was the common sign occurring in 73.5% of the patients, one (3%) had only absent ankle jerks and 8 (23.5%) had sensibility and tendon reflexes altered. Two patients had only symptoms and two had sub-clinical peripheral neuropathy with neither symptoms nor signs - the peripheral neuropathy was diagnosed by the neurophysiologic study. Thirty two (94.1%) patients were taking drugs supposed to be neurotoxic (d4T, ddI, ddC, isoniazid)²²⁻²⁵. Thirty nine patients had electroneuromyography performed. Thirteen (33.3%) of those had features of peripheral neuropathy. The types of peripheral neuropathy are shown in Table 2. Seventy five per-

Table 1. Summary of HIV-associated peripheral neuropathies, clinical manifestations and diagnosis*.

Diagnosis	HIV disease stage	Clinical symptoms	Neurological signs	Diagnostic studies
Distal symmetric polyneuropathy	Late	Distal symmetric numbness, tingling and burning sensations; paresthesias or aching	Stocking-glove sensory loss; depressed or absent ankle reflex	EMG: distal axonopathy
Inflammatory demyelinating polyneuropathy	Early>>Late	Progressive weakness; paresthesias	Muscle weakness; mild sensory loss; areflexia	CSF: lymphocytic pleocytosis (10 to 50 cells/ μ l); EMG: demyelination
Mononeuritis multiplex	Early (limited) Late (progressive)	Foot or wrist drop; facial weakness; focal pain	Multifocal cranial and peripheral neuropathies	EMG: multifocal axonal neuropathies
Progressive polyradiculopathy	Late	Lower extremity weakness; sphincter dysfunction; paresthesias	Flaccid paraparesis; saddle distribution anesthesia; depressed ankle and knee reflexes	CSF: increased PMNs; EMG: polyradiculopathy
Autonomic neuropathy	Early>>Late	Orthostatic dizziness; syncope; diarrhoea; anhidrosis; palpitations; impotence; urinary dysfunction	Orthostatic hypotension; pupillary abnormalities; sweating dysfunction; resting tachycardia	ECG: arrhythmias; blood pressure; orthostatic hypotension

CSF, cerebrospinal fluid; ECG, electrocardiography; EMG, electromyography; PMNs, polymorphonuclear leukocytes. *Reproduced from Wulff and Simpson²⁹.

cent (six patients) of the patients who had a diagnosis of DSP on electrophysiologic grounds were taking drugs supposed to be neurotoxic (d4T, ddi, ddC isoniazid)²²⁻²⁵. Laboratory analysis did not show any significant abnormalities (42 patients were tested), except in four who had VDRL positive.

DISCUSSION

To our knowledge this is the first study of the frequency of peripheral neuropathy in HIV-positive individuals in Brazil. In accordance with others²⁶ we found that 69.4% of our patients had a clinical diagnosis of peripheral neuropathy. Interestingly, 64.7% of those did not have any complaint suggesting the involvement of the peripheral nervous system. That subclinical peripheral nerve dysfunction has been described^{5,27} and may reach 71% of those examined²⁸. The most common complaints are numbness, paresthesias and painful dysesthesias^{12,29}. In our series the main symptom was mild distal dysesthesia that neither interfered with the activities of daily living nor required specific therapy. The main neurological sign was distal symmetric sensory alteration (in 97.1% of the patients) in the four limbs but mainly in the feet.

Thirteen (33.3%) of our 39 patients that had electrophysiologic testing, had features of nerve lesion. The main electrophysiologic diagnosis was sensitive-motor axonal neuropathy. In the literature DSP is responsible for 90% of the peripheral neuropathies in HIV-infected individuals^{3,12,13,16,30}. Its incidence increases with advanced immunosuppression and with decreased CD4-cell counts³¹, and thus more frequent in the later stages of the disease. DSP is clinically present in 10 to 35% of AIDS

patients without known causes for their neuropathy^{12,13,16,32}. In advanced immunosuppression (CD4 < 100 cells/ μ l) DSP has been described in 30-80% of patients^{5,12,13}. Sensory symptoms predominate, and the patients complain of numbness and paresthesias. On neurological examination there is symmetric distal sensory loss with absent ankle reflexes^{12,29}. Electrophysiological studies are most compatible with an axonal neuropathy^{12,30}, the same as we found. There is a low incidence of DSP in pediatric HIV patients³³.

We also found patients with mononeuropathy, mononeuropathy multiplex and demyelinating neuropathy (Table 2).

The etiology and pathogenesis of peripheral neuropathy associated with HIV infection is uncertain. It can be caused by the direct or indirect action of HIV and antibody production, or secondary to infections (CMV, MAC), toxic effects of certain drugs (isoniazid, vincristine, d4T, ddi, ddC), or nutritional deficiencies (vitamin B12)^{4,7,22-26,34-36}. In our study, almost all the patients that had diagnosis of peripheral neuropathy were taking drugs probably neurotoxic (ddi, d4T, ddC isoniazid).

Our electrophysiologic findings were much lower when compared to our clinical neurological evaluation. The discrepancy between our clinical and electrophysiologic findings is probably do to the well known poor evaluation of thin fiber system related to the routine nerve conduction tests³⁷.

Peripheral neuropathy in HIV seropositive patients may be overlooked or misdiagnosed. A discerning clinical analysis may be helpful in the diagnosis of this common disease since

Table 2. Clinical manifestations, electroneuromyography and diagnosis.

	Age	HIV/AIDS	Symptoms	Signs	ENMG	Evolution	Diagnosis
1	38	HIV	no	no	axonal		DSP
2	23	AIDS	yes	S/M	axonal	sub-acute	DSP
3	30	AIDS	yes	S	axonal	chronic	DSP
4	35	AIDS	yes	S/M	axonal	chronic	DSP
5	38	AIDS	no	S	axonal		DSP
6	43	HIV	yes	S	axonal	sub-acute	DSP
7	47	AIDS	yes	no	axonal		DSP
8	35	AIDS	no	S/M	axonal		DSP
9	38	AIDS	yes	S		chronic	MM
10	52	HIV	yes	S/M		chronic	MM
11	49	HIV	yes	S	demyeliantin	chronic	IDP
12	39	AIDS	yes	S	?	chronic	M
13	49	HIV	no	no	?		M

S, sensibility; M, motor; ENMG, electroneuromyography; DSP, distal symmetric polyneuropathy; IDP, inflammatory demyelinating polyneuropathy; MM, mononeuropathy multiplex; M, mononeuropathy.

the conventional electrophysiological study can underestimate some cases of peripheral nerve involvement.

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