

Clinical and diagnostic aspects of the primarily neural leprosy¹

Aspectos clínicos e diagnósticos da hanseníase primariamente neural

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Abstract

A total of 33 patients, 28 males and five females, from nine to 87 years of age, with suspected leprosy associated peripheral neuropathy, without detectable skin lesion or positive skin bacilloscopy, were studied during the period of 1994 to 2004. Patients were submitted to dermatological and neurological examination, electrophysiologic tests, Mitsuda reaction and nerve biopsy. Samples for histopathological exams were stained with hematoxylin-eosin, Faraco-Fite and immunohistochemistry with anti-BCG antibodies. Among patients with suspected leprosy, the clinical presentation of polyneuropathy occurred in 17 (51.51%) patients while 13 (39.39%) presented mononeuropathy multiplex and 3 (9.1%) mononeuropathy. The hematoxylin-eosin and Faraco-Fite stainings confirmed the leprosy diagnosis in 10 (30.30%) patients. Three patients presented a borderline pattern, two tuberculoid

pattern and no characteristic histological pattern was observed in the remaining five patients. The final classification depended on the clinical-histological correlation. Immunohistochemistry increased the diagnosis to 11 (33.33%) cases. Among the remaining 22 patients, three patients had leprosy confirmed increasing the diagnosis to 14 (42.43%) cases. One was clinically understood as a primarily neural leprosy, probably tuberculoid form of the childhood. From the remaining patients, 19 (57.57%) were excluded during the follow-up. The primarily neural leprosy (PNL) is an unusual leprosy presentation and a complex form to diagnose. The clinical follow-up accompanied by the improvement of histopathological examination of the nerve may add more accuracy to the investigation of the suspected leprosy neuropathies.

Key words: leprosy; neuropathy; nerve biopsy

Introduction

Hansen's disease is a multisystemic affection that occurs concomitantly in the skin and peripheral nerves. In the lepromatous leprosy may occur ocular, sinovial, bone, mucosal and visceral involvement. All the skin lesions show inflammatory involvement of the cutaneous nerves, nevertheless, there are leprosy cases with neurological involvement and absence of cutaneous lesions, thus, being necessary to rely on neurologists, neurophysiologists and pathologists to reach the correct diagnosis of this complex form of the disease. Such cases are initially denominated as primarily or pure neural leprosy by the Indian classification of 1955, which was maintained in 1981, when Job and Chacko suggested changes in the classification^{1,2}.

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Prevalence of primarily neural leprosy (PNL) varies from 5 a 15% according to the different types of Leprosy Attention Services, being lower in the specialized Hospitals (5%) and higher (15%) in the outpatient clinics of the Asian Services according to Van Brackel, 1994³. In the "Lauro de Souza Lima" Institute, at the Division of Rehabilitation, between the period of 1981 and 1996, 265 patients with leprosy neuropathies were attended and 4% of them had confirmed diagnosis of PNL⁴. The findings suggestive of leprosy are the demonstration of hypoaesthesia or anaesthesia in one area of the skin, or evidence of peripheral neuropathy as an isolated neuropathy form of a cutaneous branch" or in a nerve trunk, or as a multiplex mononeuropathy with sensitive and motor manifestations.

Paresthetic notalgia and meralgia are mononeuropathies to be considered in the differential diagnosis of leprosy¹. Notalgia is located in the dorsal region and results from the involvement of the primary posterior division of the intercostal nerves and meralgia results from involvement of the lateral cutaneous branches or from the anterior cutaneous femoral nerve.

On the other hand, neural involvement in leprosy may clinically resembles polyneuropathy, with generalized involvement of nerves in the extremities. This clinical presentation is mainly observed in cases with low immunological resistance, i. e., in the lepromatous and borderline lepromatous leprosy forms. The diagnosis of this manifestation is rarely difficult because it occurs in multibacillary patients in which skin lesions are more evident and bacilloscopy is positive. However, rare cases are found without characteristic skin lesions and with involvement of nerves, mainly in lower limbs that may clinically simulate a polyneuropathy resulting from the confluence of mononeuropathies.

Patients and Methods

The 33 patients evaluated were referred to the "Lauro de Souza Lima" Institute by the public health system unities (SUS) of the state of São Paulo and from other states in Brazil, in the period from 1994 to 2004. They had presented peripheral neuropathy, without skin lesions suggestive of leprosy.

Patients were evaluated through clinical dermatological, neurological and neurophysiological examination, laboratorial exams, bacilloscopy in areas with suspected lesions, bacilloscopic index, Mitsuda reaction and nerve biopsy for histopathological examination. Nerve biopsies were performed in the sural nerves of 29 patients and in the dorsal cutaneous branches of the ulnar nerves in four patients. All of them presented with loss of function confirmed clinically or by neurophysiological exams. Patients with dermatological lesions or changes of sensitivity were submitted to skin biopsy.

Patients excluded from the study were the ones suspected of leprosy, with clinical or neurophysiological presentation of proximal involvement with the following diagnosis: sporadic amiloidosis (one patient), chronic polyradiculoneuritis (one patient), siringomielic syndrome (one patient), and nerve tumors (two patients, one in the tibial nerve and the other in the medial plantar).

Patients in which skin lesions were identified during the first evaluation were also excluded from the study (three patients). Nonetheless, the PNL diagnosis was maintained when specific cutaneous lesions or positive skin bacilloscopy was detected during the follow-up.

Sensitivity mapping

The Semmes-Weinstein group of six nylon monofilaments was used to evaluate cutaneous sensitivity of upper and lower limbs. Monofilaments are constituted of 38 mm long nylon wires with different diameters, with force variations of 0,05g, 0,2g, 2,0g, 4,0g, 10,0g e 300g⁸.

When perpendicularly applied to the skin and suffering a slight curvature, each monofilament exerts a specific force on the tested area that allow us to evaluate and quantify the threshold of tactile and pressure perception. Each one of the filaments is associated with a functional level⁹.

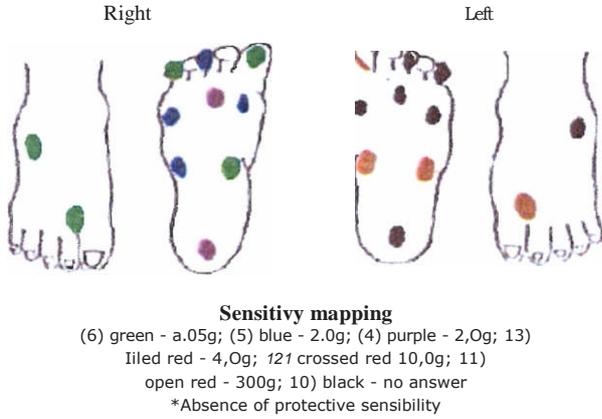
The test was performed on the sensitive distribution of the medial, ulnar, radial, tibial, fibular and sural nerves. Results were used to register the number of nerves involved and helped to define the clinical picture in mononeuropathy, mononeuropathy multiplex and polyneuropathy.

Neurophysiologic study

The electroneuromyography exam (ENMG) was guided by clinical findings and by changes detected during sensitivity mapping, sometimes it was done in the four limbs, sometimes it was limited to the evaluation of sensitive nerves to orient the biopsy. Sural nerves were always examined through the antidromic technique with the surface receptive electrode of 9 mm diameter disks, in a distance of 23 mm (center to center) between the active and reference electrodes. The electrode was placed posterior to the lateral malleolus, half a distance between the calcaneous and the fibular tendons. The ground electrode was placed on the dorsum of the foot. The stimulating cathode was located around 100 to 120 mm above the active receptive electrode¹⁰.

When neurological manifestations were located in the upper limbs, the dorsal branches of the ulnar nerves were examined¹⁰ and nerves presenting neurophysiologic changes were biopsied. The neurophysiologic changes coincided with sensitivity losses demonstrated on the sensitivity mapping (Figure 1).

Figure 1. Sensitivity mapping of feet of patient n° 28 showing areas of the left sural nerve with absence of deep sensitivity on the dorsum of the feet stained in black.



Biopsy of the sural nerve - procedure

For the biopsy of the sural nerve, a 4 to 6 cm long surgical incision was made behind the lateral malleolus, half a distance between the fibular and the calcaneous tendons.

The nerve was dissected and a fragment containing one to two fascicles (from two to three cm long) was taken. The biopsy of the dorsal cutaneous branch of the ulnar nerve was done in four patients by a hand surgeon. The fascicles collected were about 2 cm long.

Biopsy of the nerve - histopathology

Biopsied nerves were divided in three fragments of 10 to 15 mm. One fragment was fixed in FMA"

(formalin, mercury chloride and glacial acetic acid), the

other was fixed in 1% osmium tetroxide, and the last one was kept in liquid nitrogen for further studies.

Both fixed materials were included in paraffin and sectioned through conventional microtomy in 6 µm sections and stained by hematoxylin-eosin (HE). The sections of FMA fixed material were also stained by the Faraco-Fite, Gomori's trichomic, Red Congo and PAS (periodic acid of Schiff). Four µm sections were also used for immunohistochemical staining with

anti-BCG anti-body using the biotin-avidin peroxide complex^{12,13}

Since the anti-BCG antibody stains bacillary antigens, the intensity of the staining was semi-quantitative and defined in the following scale:

Results and Discussion

The clinical picture was established based on clinical aspects and on sensitivity mapping.

The neurophysiological findings in the chosen biopsy nerves showed four distinct aspects:

- a) absence of response in both sides;
- b) unilateral absence of response (Figure 2);
- c) bilaterally decreased amplitude of the sensitivity action potential (SAP), considering reference values for the age range, height and gender', and
- d) over 50% decreased amplitude of the SAP, compared with the contralateral limb (Figure 3).

Figure 2. Sensitive conduction of the sural nerves, normal in the right side, no response in the left side (patient n° 28).

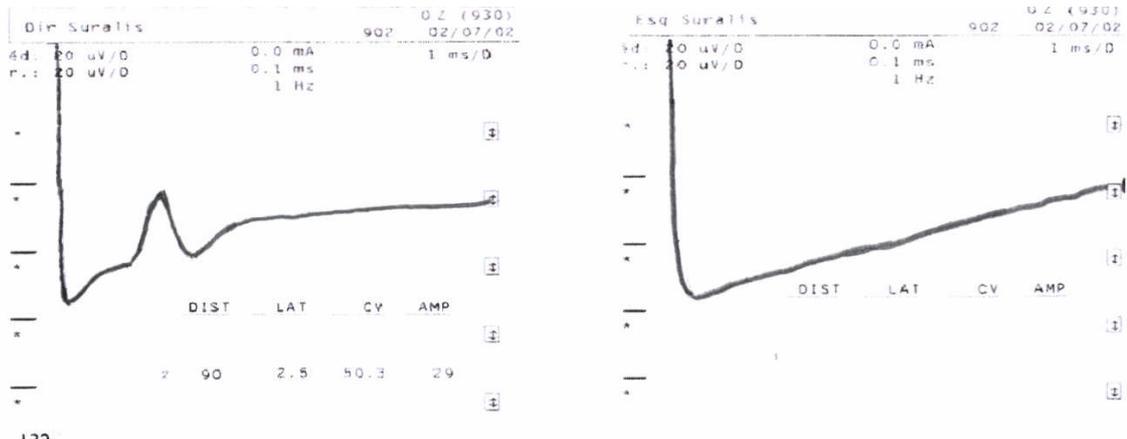
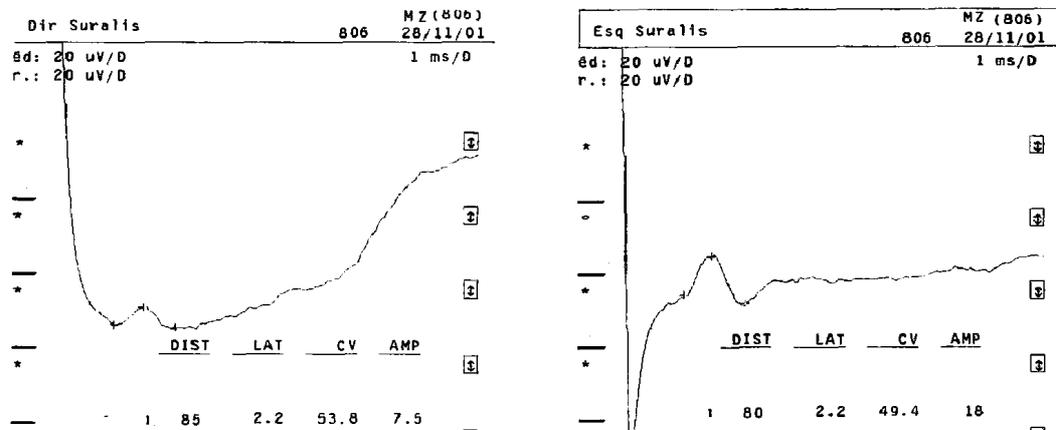


Figure 3. Sensitive conduction of the sural nerves, 50% decreased amplitude of the potential of action in the right side compared to the contra-lateral member (patient n° 8).



The histopathological leprosy diagnosis was defined in 10 patients (30,30%) through HE and Faraco-Fite staining. Immunohistochemical staining demonstrated endoneural mycobacterial antigens in ten biopsies. In one patient (n°12) the inflammatory infiltrate was unspecific and bacilloscopy was negative,

nonetheless, mycobacterial antigens were detected by immunohistochemical staining (Table 1 and Figures 4 and 5). However, in our routine, the peri or endoneural inflammatory involvement is compatible with the diagnosis of leprosy.

Figure 4. Patient no 12, a section of the sural nerve, fascicles showing peri and endoneural multifocal lymphocytic infiltrate. HE - Original magnification: 20X.

Figura 4. Paciente no 12, a seção do nervo sural, fascículos com infiltrado linfocitário multifocal, per' e endoneural. HE - aumento original: 20X.

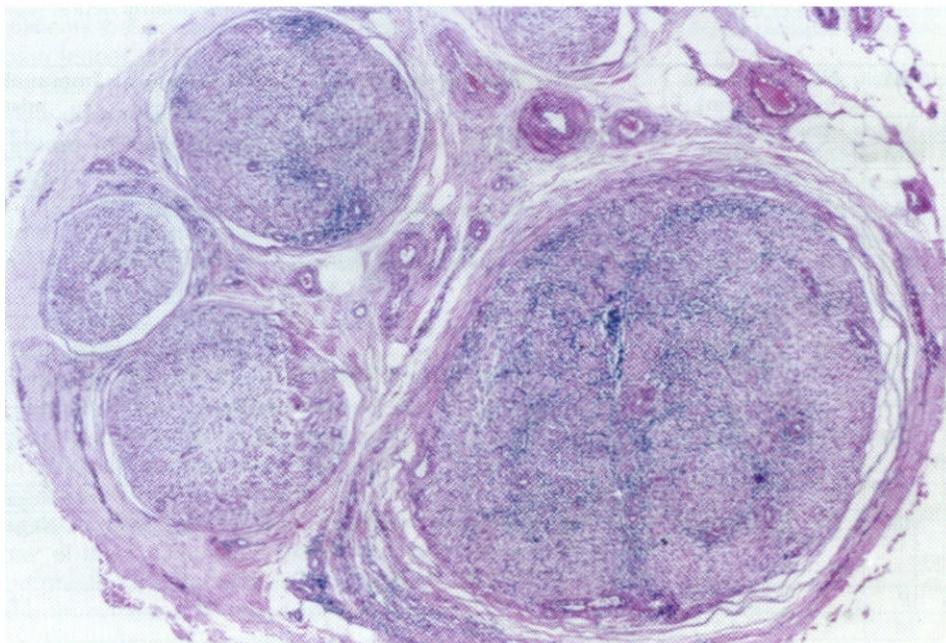
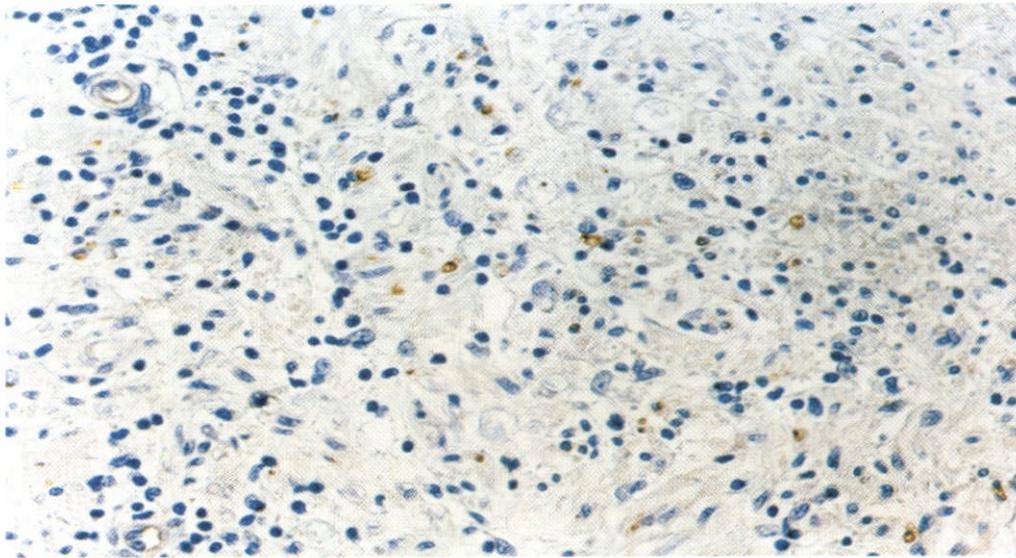


Figura 5. Patient no 12, mycobacterial antigen in endoneural location close to the lymphocitic infiltrate. Imunohistochemistry with anti-BCG - Original magnification: 160X.

Figura 5. Paciente nº 12, antígeno micobacteriano em localização endoneural ao lado de infiltrado linfocitário. Imunoistoquímica anti-BCG - aumento original: 160X.



In another three patients (n^o 4, 23 and 25) the diagnosis was accomplished during the clinical follow-up. In one patient the bacilloscopy of the skin was positive (n^o 23), in the other (n^o 25) the Mitsuda reaction clearly positive (8 mm), and during the follow-up nerve thickening was detected and the

diagnosis of other possible neuropathies was refuted (Table 1). The 9 year-old child (n^o 4) that presented fibular mononeuritis since one year old, had family history of leprosy and positive Mitsuda reaction (14 mm). During evolution, this patient didn't show any changes in the neurological picture (Table 1).

Table 1: Data about age, clinical diagnosis, number of nerves involved, Mitsuda reaction, histopathological examination, immunohistochemistry and classification of the 14 patients with diagnosis of primarily neural leprosy.

g l i 4 1
 NM = neurological manifestation; NI = nerves involved; CF = clinical form *asymmetric; **ulcerated; ***this patient presented positive skin bacilloscopy during the follow-up. M = Mononeuropathy; MM = mononeuropathy multiplex; P = polyneuropathy. 0 = absence of staining, + = rare and sparse, ++ = multiple and sparse, +++ = multiple and generalized. B=borderline, T=tuberculoid, BT= borderline tuberculoid.

Case	Age	NM	NI	Mitsuda (mm)	Histopathology of nerves	3actlloscopy of nerves	immunonistocne mistry	CF
1	26	M	1	5,0	Borderline pattern	3+	+++	B
2	74	MM	8'	10,0**	Tuberculoid pattern	0	++	BT
4	9	M	1	14,0	No changes	0	Negative	T
6	66	MM	6	5,5	Unspecific inflammatory infiltrate and demyelination	1 bacillus	++	B
7	43	MM	8*	Negative	Multibacillary leprosy and endoneural hyalinization	4+	+++	B
8	56	MM	5	Negative	Borderline pattern	4+	+++	B
9	87	P	12	Negative	Multibacillary leprosy	3 a 5+	+++	B
12	69	P	6	Negative	Peri and endoneural inflammatory infiltrate	0	++	B
22	38	P	4	3,0	Borderline pattern	3+	+++	B
23***	50	P	6	4,5	Demyelination no inflammatory infiltrate	0	Negative	B
25	34	MM	8*	8,0	No changes	0	Negative	B
28	60	MM	4'	Negative	Total demyelination, endo and perineural hyalinization compatible with residual leprosy lesions	0	Negative	B
29	47	P	8	Negative	Multibacillary leprosy	4+	+++	B
32	23	M	1	4,5	Tuberculoid pattern	0	++	T

The nodular tuberculoid leprosy of the childhood, known by the old leprologists, usually evolves with a single skin lesion and tend to improve spontaneously^{14,15}. It is relevant to point that this child presented a well-defined and stable lesion in only one nerve, that may correspond to the "pure" neural tuberculoid leprosy of the childhood.

Histopathological analysis together with the clinical manifestations allowed the classification of two patients as tuberculoid (T), one as borderline tuberculoid (BT) and 11 as borderline (B) (Table 1). Evident thickening of nerves was not detected in these patients when examined for the first time.

The Mitsuda reaction was done in all leprosy patients, eight were positive and six negative. The result of the Mitsuda reactions varied from 3,0 a 8,0 mm in six patients and were above 10 mm in two (Table 1). The primarily neural leprosy forms were unusual findings in this study whose period of data collection was long (10 years) and the number of cases was low. In 2002, the incidence of PNL at the "Lauro de Souza Lima" Institute was lower than 1%, likely because of the increased accuracy of the dermatological examination and the effective diagnosis of other peripheral neuropathies. In several patients referred for investigation and submitted to dermatological examination, characteristic leprosy skin lesions were detected; these patients were excluded from the casuistic because by definition they were not considered PNL patients. Among the patients included in the study, however, one presented visible skin lesion two months after the PNL diagnosis obtained through nerve biopsy (ng 9). Such situation has been described in the literature by several authors^{16,18}, emphasizing the little incidence of "pure" neural leprosy if the skin is carefully examined. Even patients that presented as "pure" neural leprosy develop skin lesions during the evolution of the disease. That is the reason why the authors suggest that the more appropriate denomination would be "primarily neural leprosy" instead of "pure neural leprosy", of a more absolute meaning.

In three patients only one nerve was involved, therefore, 25.90% presented features of mononeuropathy. The remaining patients had more than four nerves involved, six patients (42.85%) were classified as mononeuropathy multiplex (MM) and five (31.25%) as polyneuropathy (Table 1).

The staining with the anti-BCG antibody was positive in 10 patients, one showing nonspecific inflammatory infiltrate and negative bacilloscopy (n°12). In four patients, in which the staining was negative (n° 4, 23, 25 and 28), there wasn't inflammatory infiltrate, only demyelination in two patients (no 23 e 28). In these two cases the epicenter of the inflammatory process could have been located proximal to the biopsied site, being only the consequences evident, i. e., the demyelination distal to the lesion. The endoneural hyalinization (n° 28) is a characteristic occurrence in neural and cutaneous residual leprosy lesions.

In 19 (57.57%) patients in which leprosy diagnosis was not confirmed, the diagnosis described in the table 2 were accomplished by the clinical picture and follow-up helped by laboratory exams, electromyography and histopathology of the nerve. In endemic areas, in such cases, biopsy of the nerve is necessary, not only because of the eventual difficulties found in the effective clinical and laboratorial differentiation, but also because of the possibility of co-morbidity occurrence.

From the six patients without defined etiology, four continue to be evaluated in the out-patient clinic of the "Lauro de Souza Lima" Institute.

Table 2. Data about age, neurological manifestation, histopathological evaluation, and clinical diagnosis of the 19 patients with other neuropathies.

Case	Age	NM	Histopathology of nerves	Final diagnosis
3	67	MM	Diffuse demyelination, without inflammatory changes	No determined etiology
5	66	MM	Cicatrical vasculitis	Vasculitic neuropathy
10	62	P	No histological changes	Diabetic neuropathy
11	57	P	Without histological changes	Diabetic neuropathy
13	73	MM	Focal obliterating atherosclerosis	No determined etiology
14	67	P	Diffuse demyelination, without inflammatory changes	No determined etiology, under follow-up
15	52	P	Without histological changes	No determined etiology, under follow-up
16	49	P	Diffuse demyelination, without inflammatory changes	Alcoholism associated neuropathy
17	42	P	Without histological changes	Alcoholism associated neuropathy
18	46	P	Diffuse demyelination, without inflammatory changes	Alcoholism associated neuropathy
19	17	P	Diffuse demyelination, without inflammatory changes	Sensitive hereditary neuropathy
20	26	P	Diffuse demyelination, without inflammatory changes	Alcoholism associated neuropathy
21	76	P	Without histological changes	No determined etiology, under follow-up
24	34	P	Without histological changes	Sensitive hereditary neuropathy
26	44	MM	Without histological changes	No determined etiology, under follow-up
27	60	MM	Without histological changes	Ulnar tunnel syndrome at the elbow
30	49	MM	Without histological changes	Ulnar tunnel syndrome at the elbow
31	68	MM	Without histological changes	Ulnar tunnel syndrome at the elbow
33	41	P	Diffuse demyelination, without inflammatory changes	Alcoholism associated neuropathy

NM = neurological manifestation; MM = mononeuropathy multiplex; P = polyneuropathy. Immunohistochemistry was negative in the 19 non-leprosy neuropathy.

Conclusions

The primarily neural leprosy is a rare occurrence when the skin of patients is thoroughly examined. This way the risk of cutaneous lesions being undetected is reduced and the unnecessary biopsy of nerves avoided.

The Mitsuda reaction was negative in six (42.85%) out of 14 patients whose leprosy diagnosis was confirmed, therefore, negative Mitsuda reaction itself must not be considered a factor to exclude the primarily neural leprosy.

The anatomopathological study of nerves is an efficient tool for the diagnosis of leprosy patients without skin lesions. The techniques used may be directed to the detection of bacilli or its antigens, such as in the immunohistochemistry, in order to improve the sensitivity of the routine histopathological exam. In cases in which nerve biopsy was not conclusive, clinical follow-up of patients, i. e., dermatological and neurological examinations, bacilloscopy and histopathology of the skin, will have a preponderant role in the investigation of the patients with suspected leprosy peripheral neuropathy.

Resumo

Neste trabalho foram acompanhados clinicamente 33 pacientes com a idade de nove a 87 anos, 28 masculinos e cinco femininos, suspeitos de hanseníase, com neuropatia periférica, sem lesão de pele evidente e sem baciloscopia e biópsia de pele positivas, durante o período de 1994-2004. Todos foram submetidos aos exames dermatológico, neurológico, neurofisiológico, reação de Mitsuda e biópsia de nervo. As biópsias de nervo foram fixadas em FMA e ósmio e os

cortes histológicos corados pela hematoxilina-eosina, Fite-Faraco e imunoistoquímica com anticorpo anti-BCG. O quadro clínico de polineuropatia ocorreu em 17 (51,51%) pacientes, mononeuropatia múltipla em 13 (39,39%) e mononeuropatia em 3 (9,1%). As colorações pela hematoxilina-eosina e o Fite-Faraco foram conclusivas para hanseníase em 10 (30,30%) pacientes, três deles apresentaram padrão Dimorfo, dois padrão Tuberculóide e nos restantes cinco não havia padrão histológico característico e o diagnóstico final dependeu da correlação clínico-histológica. O estudo imunoistoquímico foi positivo em todos os casos com infiltrado inflamatório específico, e em um paciente com infiltrado inflamatório inespecífico, aumentando o diagnóstico de hanseníase para 33,33% (11). Durante o acompanhamento clínico dos 22 pacientes restantes, três tiveram o diagnóstico de hanseníase confirmado e nos demais 19 (57,57%) foi afastada a possibilidade de hanseníase, passando a 42,43% (14) os pacientes com hanseníase primariamente neural. A hanseníase primariamente neural é uma manifestação incomum da hanseníase, e o seu diagnóstico é complexo. O acompanhamento clínico em conjunto com a melhora das técnicas do exame histopatológico do nervo oferece mais acuidade para a investigação dos casos suspeitos de hanseníase primariamente neural.

Palavras-chave: hanseníase; neuropatia; biópsia de nervo

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