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SMALL-FIBER POLYNEUROPATHY IN LEPROSY WITHOUT SKIN CHANGES

Study of 17 cases

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ABSTRACT - Leprosy is one of the most common diseases of the peripheral nerves. In some cases there is only neural involvement without skin changes (neuritic form). The neuropathy has often a distal stocking and glove distribution with thermal and pinprick anesthesia and preservation of proprioception. There is no weakness, the tendon reflexes may be preserved and sometimes the nerves are thickened. We reported 17 patients with a predominantly small-fiber polyneuropathy due to leprosy. All patients had distal temperature and pain anesthesia with different individual variations. The tendon reflexes were normal in seven patients and in eight there was thickening of the nerves. The nerve conduction was normal in three patients. Sural nerve biopsy consisted of: 1) inflammatory infiltrates, 2) vacuolated "foamy" cells, 3) fibrosis of endoneurium, perineurium, and epineurium, 4) partial or total loss of nerve fibers, 5) large number of bacilli. We concluded that in countries where leprosy is frequent, nerve biopsy is an obligatory procedure in patients with predominantly small-fiber polyneuropathy.

KEY WORDS: leprosy, pure neuritic leprosy, small-fiber polyneuropathy, peripheral neuropathy, nerve biopsy.

Polineuropatia de fibras-finas devido a lepra sem alterações cutâneas: estudo de 17 casos

RESUMO - Em vários países tropicais a lepra constitui uma das principais causas de acometimento dos nervos periféricos. Em alguns casos somente os nervos são comprometidos, sem acometimento cutâneo (forma neurítica pura). Na polineuropatia há anestesia térmica e dolorosa com preservação da propriocepção. A força é normal, os reflexos profundos podem estar preservados e os nervos nem sempre estão espessados. Relatamos 17 pacientes com este tipo de polineuropatia. Todos tinham variados níveis de anestesia térmica e dolorosa distal nos membros. Os reflexos profundos estavam normais em sete pacientes e em oito havia leve espessamento dos nervos. A neurocondução foi normal em três pacientes. A biópsia do nervo sural revelou: 1) extenso infiltrado inflamatório, 2) células vacuoladas, 3) fibrose do endoneuro, perineuro e epineuro, 4) perda total ou parcial de fibras nervosas, 5) presença de bacilos da lepra. Concluímos que somente a biópsia de nervo permite o diagnóstico de pacientes com polineuropatia com acometimento predominante de pequenas fibras devida a lepra.

PALAVRAS-CHAVE: lepra, lepra neurítica pura, polineuropatia de fibras finas, neuropatia periférica, biópsia de nervo.

Leprosy is one of the most common treatable peripheral neuropathy in the world. It usually affects the skin and the nerves. It is caused by the *Mycobacterium leprosy* an acid-fast bacillus and occurs mainly in developing countries of tropical and subtropical areas. Although the prevalence of the disease is decreasing, leprosy still represents one of the major public health problems in about 80 countries within Asia, Africa and Latin America, mainly in India and Brazil[1-4]. From the clinical viewpoint there is a type of leprosy called the pure neuritic form without any skin lesions[5,6]. Patients with the "pure neuritic" form of leprosy are frequently misdiagnosed[7]. Some studies suggest that about 4 to 10 % of patients with leprosy have a pure neural involvement[8-10]. Males are significantly more affected than females[11-13].

Mononeuritis or mononeuritis multiplex are the most common presentations of this primary neuritic leprosy in previous studies[10, 11]. In patients with mo-

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noneuritis the nerve usually is enlarged and the others may appear thickened. Ulnar is the most frequently affected nerve[9,11,12]. Histologic preparations usually show changes compatible with borderline or tuberculoid leprosy[5]. In a few cases there is a distal symmetric neuropathy with temperature and pain anesthesia without muscle weakness. In these cases the tendon reflex may be retained and the electromyography (EMG) may be normal.

We describe 17 cases with this form of polyneuropathy (small-fiber polyneuropathy- SFP) without skin lesions, that only after sural nerve biopsy, could a diagnosis of leprosy be established.

METHOD

From January 1995 to May 2002 we studied 17 patients with SFP probably due to leprosy. There were no other known etiologies for the polyneuropathy. Patients were referred to our Neuromuscular Unit at Antonio Pedro Hospital from the Federal Fluminense University in Niterói city of Rio de Janeiro State. All 17 cases included in this study were adults and they ranged in age from 21 to 80 years and only three of them were females. In addition to clinical examination, dermatologic examination, investigations such as skin smears, Mitsuda tests and EMG studies were carried out. In all of them appropriate investigations were done to exclude other causes of small-fiber polyneuropathy. We performed sural nerve biopsy in all cases.

The specimen was fixed in 3% glutaraldehide, stained with hematoxilin & eosin (H&E), Gomori's trichrome, Congo red and Wade's for bacilli identification. Semi-thin sections were stained with toluidine-blue. When necessary, ultra-thin sections were examined under an electron microscope.

RESULTS

Muscle strength and bulk was normal in all cases. The tendon reflex were normal in seven patients and decreased or absent in lower limbs in ten cases. All patients had distal temperature and pain anesthesia with different individual variations. Two patients had a sensory level in C6. In eight cases there was a mild multiple uniform thickening of the peripheral nerves (Table 1). In the other nine patients there were no nerve enlargements. Examination of the entire cutaneous surface failed to reveal any lesions suggestive of leprosy. Skin smear was negative for acid-fast bacilli in all the patients. The Mitsuda test was positive in 14 cases. The motor and sensory nerve conduction was within normal limits in three

Table 1. Characteristics of patients with small-fiber polyneuropathy due to leprosy.

Number	Age (Years)	Sex	Muscle strength	Tendon jerks	Temperature/ pain anesthesia	Nerve thickening	Nerve conduction
1	72	M	N	N	LL	N	SNAP 0 MUAP+ LL
2	69	M	N	N	LL	N	N
3	46	M	N	N	LL	N	SNAP 0 LL
4	80	F	N	AJ 0	LL	++	SNAP 0 MUAP+ LL
5	52	M	N'	N	LL	++	N
6	40	M	N	AJ +	LL and UL	N	SNAP 0 LL
7	64	M	N	AJ +	LL	N	SNAP 0 LL
8	21	M	N	KJ/AJ +	LL and UL	++	SNAP 0 MUAP+ LL/UL
9	43	M	N	N	LL and UL	++	SNAP 0 MUAP+ LL/UL
10	44	M	N	AJ +	LL	N	SNAP 0 LL
11	44	M	N	N	C6 level	++	SNAP 0 MUAP+ LL/UL
12	67	F	N	KJ/AJ +	LL and UL	N	SNAP 0 LL
13	61	M	N	KJ/AJ 0	C6 level	++	SNAP 0 MUAP+ LL/UL
14	71	M	N	KJ/AJ +	LL and UL	N	SNAP 0 MUAP+ LL/UL
15	62	M	N	KJ/AJ 0	LL	++	SNAP 0 LL
16	32	M	N	KJ/AJ 0	LL	++	SNAP 0 LL/UL
17	61	F	N	N	LL	N	N

M, man; W, woman; N, normal; AJ, ankle Jerk; KJ, knee jerk; LL, lower limbs; UL, upper limbs; SNAP, sensorial nerve action potential; MUAP, motor unit action potential; 0, absence; + diminished; ++ mild.

Table 2. Sural nerve biopsy findings.

Number	Inflammatory cells	Fibrosis	Nerve fiber loss	Presence of bacilli
1	+++	+++	T	+++
2	++	++	++	+
3	+++	+++	T	+++
4	+++	++	T	++
5	+++	++	T	++
6	+++	+	++	++
7	+++	+++	T	++
8	++	++	++	++
9	+++	++	T	++
10	++	++	T	++
11	+++	++	T	++
12	+++	++	T	++
13	++	++	T	+
14	++	++	T	+
15	+++	++	++	+++
16	+++	++	++	++
17	+++	++	T	+++

+ mild; ++ moderate; +++ severe; T, total loss of fibers.

cases. In the other cases the amplitude of the motor unit action potential (MUAP) or the sensory nervous action potential (SNAP) was low or absent, suggesting axonal degeneration.

In Table 2 we can see the main histopathological findings: 1) moderate to severe infiltrates consisting of macrophages, plasma cells and lymphocytes (Fig 1A and B, Fig 2A), 2) presence of vacuolated "foamy cells", 3) mild to severe fibrosis of endoneurium, perineurium and epineurium (Fig 2B), 4) partial or total loss of nerve fibers (Fig 3A), 5) large numbers of bacilli in the endoneurium, endothelial cells and particularly in the Schwann cells (Fig 3B).

DISCUSSION

Primarily neuritic leprosy is an uncommon presentation in patients infected with *Mycobacterium leprae.* We report 17 patients who manifested a predominantly SFP due to leprosy confirmed by sural nerve biopsy. In this series all except three were males. Male preponderance in neuritic group has been noticed by others as well[3,8-10,12]. Mononeuritis is the most common presentation of the neuritic form of leprosy and the ulnar nerve is the most affected. We had shown that in these cases the biopsy of the superficial ulnar nerve in the hand is the best way to diagnose leprosy[14].

The polyneuritic form is not well described. It seems that the small fibers are most involved as occurred in our cases. In some of our patients tendon reflexes were diminished or absent (10 cases) and the nerve conduction findings showed concomitant involvement of large myelinated fibers (14 cases), although there was no proprioceptive loss. In seven patients tendon reflexes were normal and in three the nerve conduction studies were also normal. We consider our cases as "pure" small fiber polyneuropathy. There are rare cases in which the polyneuropathy is of large fibers, with touch and proprioceptive loss. In these patients there were performed lumbar sensory ganglion biopsy that showed inflammatory infiltrate in severely disabled patients[15]. In one case there was a sensory-motor polyneuropathy[16]. The patient described by Gadoth et al. had a SFP with prominent autonomic disfunction[7]. There was thickening of nerves in eight of our patients. The proportion of nerve thickening by most studies in neuritic leprosy ranges from 40 to 75 %[8-13,17]. However, almost all authors[8-13,17] included cases of mononeuritic, mononeuritic multiplex and polyneuritic forms of leprosy. We described only the polyneuritic form of presentation in which we believe nerves were not enlarged in a almost a half of the cases.

Diabetes is the most common etiology of a painful, distal, symmetrical, primarily sensory polyneuropathy, sometimes with predominantly involvement of small-fibers[18]. Our patients number 11 and 17 were also diabetic. The familial amyloid polyneuropathy, not uncommon in Brazil, is another kind of polyneuropathy that can give a clinical picture similar to our cases of leprosy polyneuropathy. However in diabetes and amyloidosis there is also an autonomic neuropathy involving bowel, bladder and circulatory reflexes[18].

Mitsuda skin test did not help very much in the diagnosis. Only 3 of our patients were Mitsuda test negative, although the sural nerve biopsy findings were consistent with lepromatous leprosy. Other studies have shown similar results[3,12,19].

Our cases could be classified as lepromatous leprosy, borderline lepromatous or multibacillary form by the findings of the sural nerve biopsy: intense inflammatory infiltrates, absence of granuloma and the presence of large numbers of bacilli. Nowadays, the pure neuritic form is known to remain a distinct group in the Ridley-Jopling classification[5,10,12,16,20].

The absence of skin involvement in our cases made necessary the performance of a nerve biopsy care-

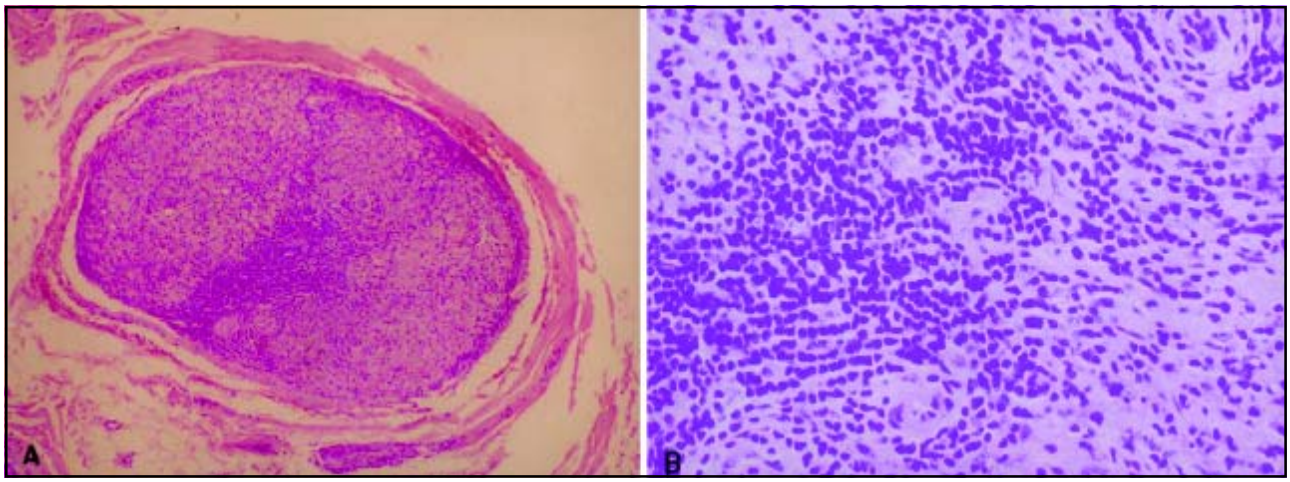

Fig 1. Sural nerve biopsy: A) Intense mononuclear inflammatory infiltrate in the endoneurium, perineurium and perineurium (H&E X 100). B) Other microscopic field shows an infiltrate in higher magnification (HE X 400).

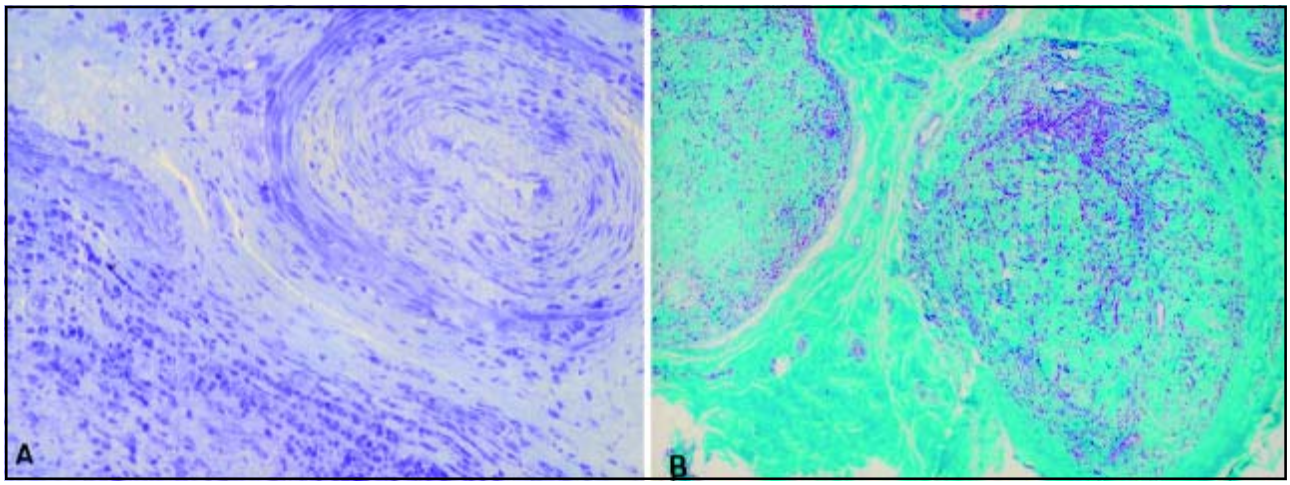

Fig 2. Sural nerve biopsy: A) Endoneural mononuclear infiltrate (toluidine blue X 400). B) Fibrosis and thickness of the endoneurium, perineurium and epineurium (Gomori's trichrome X 100).

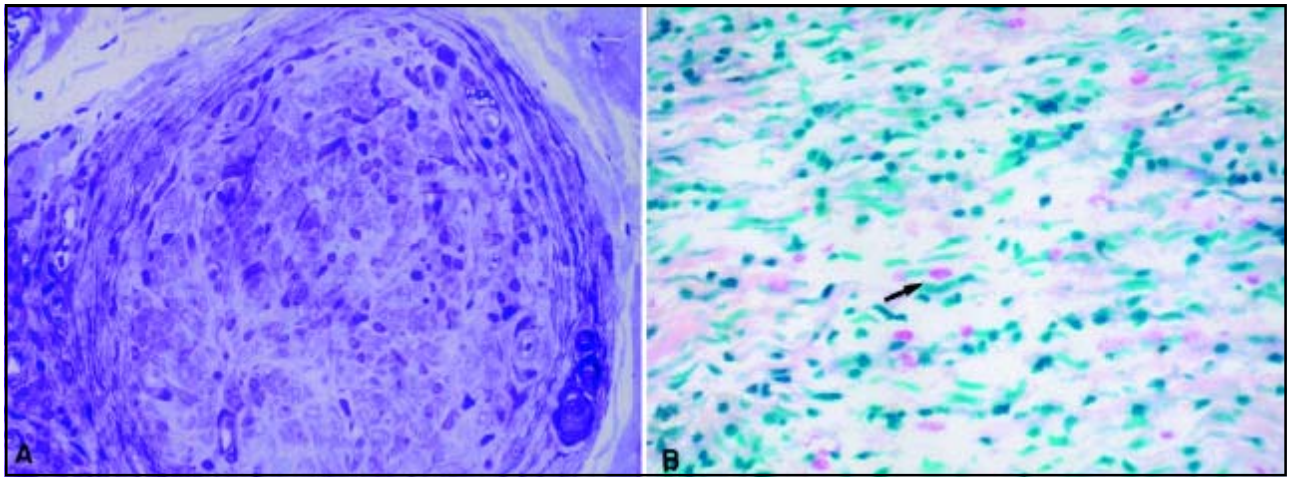

Fig 3. Sural nerve biopsy: A) Total loss of fibers (toluidine blue X 400). B) Abundant acid-fast bacilli are seen, many arranged in so-called "globi"(arrow) (Wade's X 1000).

fully looking for acid-fast organisms. The findings in all cases were consistent with lepromatous or borderline lepromatous changes[5,21,22]: severe cellular inflammatory infiltrates consisting of macrophages, plasma cells and lymphocytes, mild to moderate fibrosis, partial or total loss of nervous fibers and in adequate staining large numbers of bacilli, sometimes arranged in "globi" and, in some cases, the presence of "foamy" cells. As all of our cases were of symmetric predominantly small-fiber neuropathy, we did not see changes correlating with tuberculoid or borderline tuberculoid leprosy.

We did not perform skin biopsy in our cases considering the absence of visible skin patches. Suneetha et al.[23] performed nerve and skin biopsy in their 196 patients with pure neuritic leprosy. All patients exhibited in their nerves a spectrum ranging from tuberculoid to lepromatous leprosy. In a few cases they found histological changes in the skin. In their 77 cases of neuritic form of leprosy Jacob and Mathai[24] found negative skin biopsy and in half of the patients, leprosy was confirmed by nerve biopsy. Kumar et al.[25] studied concurrent skin and nerve biopsies in 27 patients with leprosy (with skin changes). They concluded that nerve biopsy is more informative and specific than skin biopsy in the diagnosis of leprosy. There were higher incidence of viable bacilli within the nerve as compared to skin in patients with multibacillary leprosy studied by Shetty et al[26].

We conclude that in tropical countries where leprosy is endemic, peripheral nerve biopsy is one of the best procedures for patients with SFP without skin changes for the diagnosis of leprosy.

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