

# Persistent Neuropathy in Lepromatous Leprosy Patients

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## Research Article

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# Abstract

Lepromatous leprosy (LL) patients have evidence of extensive peripheral nerve damage as soon as a diagnosis is made, but most of them have few or no symptoms related to peripheral neuropathy. Usually, they do not have the cardinal signal of leprosy neuritis. However, disability caused by peripheral nerve injuries has consequences throughout the entire life of these patients and the pathophysiological mechanisms of nerve damage are still poorly understood. The objective of this study was to evaluate the outcome of peripheral neuropathy in a group of LL patients in an attempt to understand the mechanisms of nerve damage. We evaluated medical records of 14 LL patients that had undergone a neurological evaluation at the beginning of Leprosy treatment then worsened at least 4 years after the end of treatment and underwent nerve biopsy. The symptoms at the beginning of treatment were compared with those at the time of the biopsy. Pain was a symptom in only one patient at the beginning and was a complaint in 9 patients by the time of biopsy. Neurological examination showed that the majority of patients already had alterations in medium and large caliber fibers at the beginning of the treatment, and pain increased by the time of biopsy, while neurological symptoms and signs deteriorated independently of the use of prednisone or thalidomide. Nerve Conduction Studies demonstrated that sensory nerves were the most affected. LL patients can develop a silent progressive degenerative peripheral neuropathy, which continues to develop despite high dose long term corticoid therapy.

## Introduction

Leprosy is one of the leading causes of nontraumatic neuropathy in the developing world and one of the classical examples of infectious neurodegenerative diseases of the peripheral nervous system<sup>1</sup>.

The disabilities caused by peripheral nerve damage are responsible for the stigma of leprosy. Leprosy neuropathy could lead to life-long functional and/or social disability, therefore, early detection and treatment of the neuropathy is a top priority in leprosy. Neuropathy in Lepromatous (LL) patients usually progresses silently with widespread involvement of skin and nerves<sup>1,2</sup>. Some authors reported that, in terms of Nerve Conduction Studies (NCS), LL patients worsened overall, and abnormalities persisted despite improvement of skin lesions following multidrug therapy (MDT), even in patients without evident neuritis<sup>3-5</sup> or in those who were treated with corticosteroids<sup>5</sup>.

In spite of advances in the understanding of mechanisms underlying leprosy neuropathy, many questions related to pathophysiology remain unanswered. This comprehension is necessary for early detection of peripheral nervous lesions, for the investigation of new drugs for treatment and to reduce functional disabilities in these patients. The aim of this study was to evaluate neuropathy in a group of LL patients with neurological dysfunction, years after the conclusion of MDT.

## Material And Methods

### Patient Selection:

This is a retrospective study performed by assessment of patients' medical records and a descriptive observational study of LL diagnosed patients who worsened at least 4 years after the end of MDT and underwent nerve biopsy.

Over a period from 1990 to 2006 a total of 436 LL diagnosed patients were admitted to the Leprosy Outpatient Clinic in Oswaldo Cruz Institute, Rio de Janeiro, RJ, Brazil. Neurological evaluation was not routinely performed on any of these patients upon admission because most of them did not have neurological complaints. All of them were evaluated for disability grade. Of the total, 243 who had neurological complaints and clinical signs or suspicion of nerve damage were sent to a neurologist for further examination. Twenty of them performed nerve biopsies because the neurological function worsened at least five years after MDT, in spite of corticotherapy. Fourteen of these patients were included in this study because they had a neurological examination at the beginning of the MDT.

Patients with comorbid diseases that could develop peripheral neuropathy, such as diabetes mellitus, vasculitis, hypothyroidism, rheumatological diseases, HIV, among others, were excluded.

The research was carried out in compliance with the International Norms on Ethics in Human Research, having been previously approved by the Ethics Committee of the Oswaldo Cruz Foundation (Approval number: 3.152.162). All patients voluntarily provided written informed consent.

## **Clinical evaluation**

Patients were submitted to clinical examinations for leprosy diagnosis, according to the protocol of the Leprosy Outpatient Unit of the Oswaldo Cruz Institute (8) and all patients were diagnosed with the lepromatous form.

Based on World Health Organization (WHO) guidelines<sup>6,7</sup>, according to the results of their slit-skin smears and skin histopathology, they received fixed-dose multibacillary (MB) MDT. Over the 16-year period of this review, the duration of MDT changed according to public health policies, thus some patients underwent 24 monthly doses of treatment (4 patients) and others underwent 12 monthly doses (10 patients). Upon completion of MDT, patients received health-care information, were kept under surveillance for a period of 5 years and were asked to return if any neurological symptoms appeared or new skin lesions developed.

Patients were submitted to clinical examinations for leprosy diagnosis, according to the protocol of the Leprosy Outpatient Unit of the Oswaldo Cruz Institute<sup>8</sup>.

Neurologic examinations recorded the number and distribution of affected peripheral nerves to evaluate nerve function impairment (NFI). Sensory impairment (tactile sensation, mechanical nociception, and cold thermo sensation) and/or motor deficit of bilateral trigeminal, median, ulnar, radial, sural, superficial peroneal and plantar nerves were assessed via standard methods. In brief, the tactile threshold was tested with Semmes-Weinstein monofilaments. The monofilaments vary in thickness (1 = 300g, 2 = 4g, 3 = 2g, 4 = 0,2 g, e 5 = 0,05g); and the inability to perceive the touch of even one of them represents an absence of tactile sensitivity to given pressure. Thermal sensation was determined by the use of cold metal (15°C) objects and a safety pin was utilized to ascertain pain perception in bilateral trigeminal, median, ulnar,

radial, sural, superficial peroneal, and plantar nerves. There was no data about vibratory and proprioceptive sensitivity in patient's medical records. Individual muscle strength of the upper and lower extremities was determined by voluntary muscle testing<sup>9</sup>. Disability grade was recorded in accordance with the standard WHO grading criteria<sup>10</sup>. NFI was defined as clinically detectable impairment of the motor and/or sensory functions<sup>2</sup>.

Due to the lack of information on vibratory and proprioceptive sensitivity, we classified the changes in the neurological exam as follows: small fiber damage, when there was a change in thermal and / or painful sensitivity; and medium fiber damage when there was a change in tactile, thermal and painful impairment.

## **Electrophysiologic evaluation**

Electrophysiological testing was performed with patients in supine position using the Neuropack 2 EMG measuring system (Nihon Kohden Corp., Tokyo, Japan) in accordance with standard procedures<sup>11</sup>. Skin temperature was measured at the wrists and ankles and was above 33°C. Room temperature ranged between 29°C and 32°C. Nerves were evaluated bilaterally notwithstanding the presence of clinical signs or symptoms of nerve impairment.

Amplitude, velocity, and latency were recorded for the median, radial, ulnar, superficial peroneal and sural sensory nerves in addition to the median, ulnar, tibial and peroneal motor<sup>12</sup>.

To evaluate the extent of nerve involvement, neuropathy was classified according to the number of impaired nerves and the distribution of impairment in the NCS. Polyneuropathy (PNP) was defined as such when there were diffuse lesions of peripheral nerves. Mononeuropathy (MNP) and Multiple Mononeuropathy (MMP) were diagnosed when a single nerve and focal involvement of two or more nerves occurred, respectively<sup>13</sup>.

Based on the results of the compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs), the categories of nerve segment lesion pathophysiology were defined by combining the NCS parameters. As changes in the peripheral nerves of leprosy patients are known to occur asymmetrically, like multiple mononeuropathies that converge in an asymmetric polyneuropathy (mosaic neuropathy), we evaluated nerve conduction of each nerve separately to classify the type of change. Briefly, an axonal lesion was defined as either an isolated reduction in amplitude equal to or greater than 30% of the reference values, or an amplitude reduction of less than 30% combined with 60-75% reduction in the conduction velocity of these values. Demyelination was verified as a 20% or higher increase in latency, a greater than 35% reduction in conduction velocity, or a combined reduction in amplitude of up to 20% together with 15-20% increased latency; demyelinating lesions with axonal degeneration was determined by the presence of axonal and demyelinating lesions within the same nerve. A lesion was considered as having "no conduction" when action potentials could not be recorded. Partial conduction block (CB) was defined as a 50% or higher reduction in the proximal compared with the distal amplitudes<sup>12</sup>. Here, we did not have enough data to classify temporal dispersion in the analyzed exams.

Table 1 shows the NCS normative data used in our service.

Table 1  
– Normative data of Nerve Conduction Studies

<b>Sensory</b>	<b>Amplitude (μV)</b>	<b>Lantecy (ms)</b>	<b>Velocity (m/s)</b>
Radial	8.0	2.4	41.0
Median	15.0	3.4	42.0
Ulnar	8.0	2.6	43.0
Sural	7.0	3.5	38.0
Superficial peroneal	5.0	3.5	38.0
<b>Motor</b>	<b>Amplitude (mV)</b>	<b>Latency (ms)</b>	<b>Velocity (m/s)</b>
Median	4.0	3.7	52.0
Ulnar	4.0	3.2	55.0
Common peroneal	2.0	4.5	42.0
Tibial	4.0	4.5	43.0

Sensory nerve was biopsied according to clinical or electrophysiological findings. The following nerves were evaluated: dorsal cutaneous ulnar on the dorsum of the hand (n= 7), sural nerve at the ankle level (n= 6) or superficial peroneal nerve at distal third of the leg (n= 1). Nerve samples were analyzed according to standard methods<sup>14</sup>.

## Statistical analysis

Contingency tables were constructed and data were analyzed using the McNemar test to compare neurological evaluation at the beginning of MDT and by the time of biopsy. Mean and standard deviation were calculated for continuous variables (age and basculosopic index) and Mann Whitney test was used. For comparative analysis of the NCS, a non-parametric Wilcoxon test was used. For clinical eletrophysiological comparison, Fisher's test and Chi-square was used. Significance level of 5% was adopted.

## Results

**LL patients might present alterations in medium and large caliber fibers at diagnosis independent of neural clinical signs.**

Table 2 describes the demographic and clinical characteristics of patients recruited for this study at the beginning of MDT and by the time of biopsy. The time between beginning MDT and biopsy ranged from 4 to 16 years (mean 8.14 years). Ten patients were male (71.4%), with ages ranging from 19 to 46 years (mean age 32.38 years) at the beginning of treatment, and ranging from 31 to 61 years (mean age 40.9 years) by the time of biopsy. According to the WHO grading system, 46.1% of patients were included as grade 0 (n=6). At the evaluation at the time of the nerve biopsy most patients were classified as grade 1

(46.1%). The average bacilloscopic index (BI) at the beginning of treatment was 3.95 (2.16 - 4.83) and dropped significantly to an average of 1.0 (0 - 2.85) at the time of the biopsy, confirmed by Mann Whitney test ( $p = 0.003$ ).

Table 2  
Demographic and Clinical characteristics of recruited patients at the beginning of MDT

<b>Demographic Characteristics</b>	<b>At the beginning of MB treatment</b>	<b>At the time of biopsy (neural damage)</b>
<b>Age - years mean (min-max)</b>	32.38 (19-46)	40.9 (31-61)
<b>Gender</b>		
Male	10 (71.4%)	10 (71.4%)
Female	4 (28.6%)	4 (28.6%)
<b>Disability grade</b>		
<b>0</b>	6 (46.1%)	5 (38.5%)
<b>1</b>	4 (30.8%)	6 (46.1%)
<b>2</b>	3 (23.1%)	2 (15.4%)
<b>bacilloscopic index mean (min-max)</b>	3.95 (2.16-4.83)	1.00 (0-2.25)
<b>Time between beginning MDT and worsening of neural damage in years (min-max)</b>		8.14 (4-16)
<b>Clinical Characteristics</b>		
<b>Symptoms (peripheral nerve related)</b>		
No symptoms	4 (28.6%)	0 (0%)
Pain	1 (7.1%)	9 (64.3%)
Paresthesia	6 (42.9%)	9 (64.3%)
Numbness	4 (28.6%)	1 (7.1%)
<b>Signs (peripheral nerve related)</b>		
No signs	1 (7.1%)	0 (0%)
Painful and/or thermal impairment	2 (14.3%)	1 (7.7%)
Tactile impairment	6 (42.9%)	5 (35.7%)
Motor	3 (21.4%)	5 (35.7%)
Missing info	2 (14.3%)	3 (23.1%)
<b>Thickening</b>		
Yes	9 (64.3%)	8 (57.1%)
No	4 (28.6%)	4 (28.6%)

<b>Demographic Characteristics</b>	<b>At the beginning of MB treatment</b>	<b>At the time of biopsy (neural damage)</b>
Missing info	1 (7.1%)	2 (14.3%)

Symptoms at the beginning of treatment were compared with those at the time of the biopsy using the McNemar test and only pain showed a significant difference ( $p = 0.006$ ). Paresthesia and numbness did not show significant differences ( $p = 0.102$  and  $p = 0.371$ , respectively). In relation to the signs of involvement of the peripheral nerve, we were only able to evaluate thickening by the McNemar test, which showed no significant difference ( $p = 0.317$ ). Neurological examination showed that the majority of patients already had alterations in medium and large caliber fibers since the beginning of the treatment (64.3%), which increased to 71.4% of patients at the time of biopsy (Table 2).

Table 3 describes signs and symptoms of each patient at the beginning of MDT and at the time of the biopsy, as well as the time of MDT and the amount of prednisone and thalidomide to treat the reactions and neuritis that the patients had during the entire follow-up period.

Table 3

– Comparison of signs, symptoms and treatment of each patient at the beginning of MDT and by the time of biopsy

<b>Neurological Evaluation at the beginning of MDT</b>										
<b>Patient</b>	<b>Gender</b>	<b>Age</b>	<b>Pain</b>	<b>Parest</b>	<b>Tact NFI</b>	<b>Therm NFI</b>	<b>Painf NFI</b>	<b>Mot NFI</b>	<b>MDT (Mon)</b>	<b>Tim B-B (y)</b>
AJR	MALE	45	NO	NO	YES	NO INFO	NO INFO	NO INFO	24	7
ALCF	MALE	25	NO	YES	NO	YES	YES	NO	24	11
NMC	MALE	28	NO	YES	YES	YES	YES	NO	24	4
ALRS	MALE	19	NO	NO	YES	YES	YES	NO	24	12
NMS	MALE	45	NO	YES	YES	YES	YES	YES	12	16
LGPA	MALE	23	NO	YES	YES	YES	YES	NO	12	9
RJRF	MALE	46	NO	YES	YES	NO	YES	NO INFO	12	8
CDO	MALE	31	NO	NO	YES	YES	YES	YES	12	6
SFV	FEMALE	35	YES	YES	YES	YES	YES	NO	12	8
MAP	FEMALE	31	NO	NO	YES	YES	YES	NO	12	8
MVR	FEMALE	41	NO	NO	NO	YES	NO	NO	12	4
VST	MALE	28	NO	NO	YES	YES	YES	YES	12	7
ASA	MALE	31	NO	NO	NO	NO	NO	NO	12	6
APAF	FEMALE	34	NO	NO	YES	YES	YES	NO	12	8
<b>Neurological Evaluation by the time of biopsy</b>										
<b>Patient</b>	<b>Age</b>	<b>Pain</b>	<b>Parest</b>	<b>Tact NFI</b>	<b>Therm NFI</b>	<b>Painf NFI</b>	<b>Mot NFI</b>	<b>PDN (mg)</b>	<b>TLD (mg)</b>	
AJR	52	YES	YES	YES	NO INFO	NO INFO	NO INFO	6249	18000	
ALCF	36	YES	YES	NO	YES	YES	NO	2315	NO	
NMC	33	YES	YES	YES	YES	YES	NO	44030	29200	
ALRS	31	NO	YES	YES	YES	YES	NO	24265	NO	
NMS	61	YES	YES	YES	YES	YES	YES	19490	142600	
LGPA	32	YES	YES	NO	NO	YES	NO	20190	259400	
RJRF	54	YES	YES	YES	YES	YES	YES	27165	210736	

Neurological Evaluation at the beginning of MDT									
CDO	37	NO	NO	YES	YES	YES	YES	9015	73100
SFV	43	YES	NO INFO	NO INFO	NO INFO	NO INFO	NO INFO	57555	4500
MAP	39	YES	NO	YES	YES	YES	NO	24865	145500
MVR	45	NO	YES	YES	YES	YES	NO	NO INFO	NO INFO
VST	35	YES	YES	YES	YES	YES	YES	7600	297400
ASA	37	YES	YES	YES	YES	YES	YES	39740	297400
APAF	42	NO	NO	YES	YES	YES	NO INFO	32580	25500
Parest – paresthesia; Tact NFI – Tactile nerve function impairment; Therm NFI – thermal nerve function impairment; Painf NFI – painful nerve function impairment; Mot NFI – motor nerve function impairment; MDT (Mon) – time of MDT in months; PDN (mg) – total dose of prednisone until biopsy in milligrams; TLD (mg) - total dose of thalidomide until biopsy in milligrams; TIM B-B (y) – time between beginning of leprosy treatment and biopsy; NO INFO – no information									

**Nerve Conduction Studies (NCS) demonstrate that sensory nerves were the most affected in LL patients.**

All patients were submitted to NCS by the time of biopsy, but only 8 out of the 14 patients underwent NCS at some point during the follow-up, not necessarily at the beginning of treatment, but years before the biopsy. The other 6 were submitted to NCS just before the biopsy.

Table 4 compares the average values of the first NCS performed years before the biopsy with those at the time of the biopsy by nerve studied.

There was significant worsening of sensory amplitude and sensory conduction velocity values, by the time of biopsy than in previous years, as well as an increase in the percentage of abnormal exams.

Table 4  
– Mean values of NCS and percentage of abnormality

Electrophysiological function	Normal Value	First NCS (n=16)			Pre biopsy NCS (n=28)			P value
		Mean	Range	% abnormal	Mean	Range	% abnormal	
<b>Motor Function</b>								
<b>Ulnar Nerve</b>								
Distal Latency (ms)	<3.2	2,9	2.5-3.5	22%	3.3	2.1-6.5	39.3%	0.88
NCV (m/s)	>55.0	55.6	47-60.4	43.75%	53.8	20.8-65.5	53.6%	0.55
Amplitude (mV)	>4.0	5.9	0.35-11.2	12.5%	5.1	0.29-9.44	32.1%	0.24
<b>Median Nerve</b>								
Distal Latency (ms)	<3.7	3.9	3.1-5.6	40%	3.7	3.8-5.4	39.3%	0.39
NCV (m/s)	>52.0	53.9	48-61.9	31.2%	52.5	43.3-66.5	53.6%	0.48
Amplitude (mV)	>4.0	5.5	2.1-10.1	25%	7.3	0.39-13.5	14.3%	0.026
<b>Common peroneal nerve</b>								
Distal Latency (ms)	<4.5	3.7	0-5.9	40%	3.9	0-9.4	20.8%	0.31
NCV (m/s)	>42.0	43.5	0-60	25%	37.8	0-55.3	50%	0.22
Amplitude (mV)	>2.0	3.3	0-5.9	18.7%	2.7	0-9.4	45.9	0.06
<b>Tibial Nerve</b>								
Distal Latency (ms)	<4.5	NR	NR	NR	4.6	0-6.25	58.8	NR
NCV (m/s)	>43.0	NR	NR	NR	NR	NR	NR	NR
Amplitude (mV)	>4.0	NR	NR	NR	5.3	0.18-14.8	43.7%	NR
<b>Sensory Function</b>								
<b>Ulnar Nerve</b>								
Latency (ms)	<2.6	1.84	0-2.78	20%	0.7	0-2.7	78.6%	0.89
NCV (m/s)	>43.0	41.6	0-56.6	37.5%	14.0	0-60.6	75%	0.002
Amplitude (µV)	>8.0	11.2	0-21.7	31.2%	2.6	0-16.6	85.7%	0.001

Electrophysiological function	Normal Value	First NCS (n=16)			Pre biopsy NCS (n=28)			
<b>Median Nerve</b>								
Latency (ms)	<3.4	2.1	0-2.9	20%	1.7	0-3.8	50%	0.91
NCV (m/s)	>42.0	44.4	0-61.2	25%	26.9	0-57.9	50%	0.006
Amplitude (μV)	>15.0	18.2	0-42.7	43.7%	6.4	0-26.9	85.7%	0.001
<b>Radial Nerve</b>								
Latency (ms)	<2.4	1.2	0-2.4	30%	1.2	0-3.02	71.4%	0.91
NCV (m/s)	>41.0	35.9	0-61.7	37.5%	21.7	0-52.6	67.8%	0.002
Amplitude (μV)	>8.0	9.3	0-18.3	25%	4.85	0-19.2	67.8%	0.005
<b>Sural Nerve</b>								
Latency (ms)	<3.5	0	0	100%	0.41	0-3.3	85.7%	0.18
NCV (m/s)	>38.0	0	0	100%	6.9	0-56.2	85.7%	0.18
Amplitude (μV)	>7.0	0	0	100%	0.9	0-17.1	92.8%	0.18
<b>Superficial peroneal Nerve</b>								
Latency (ms)	<3.5	NR	NR	NR	0	0	100%	NR
NCV (m/s)	>38.0	NR	NR	NR	0	0	100%	NR
Amplitude (μV)	>5.0	NR	NR	NR	0	0	100%	NR
NCS = nerve conduction study; NR = not realized; ms (milliseconds); mV – millivolt; μV = microvolt; m/s = meter per second; n = number of nerves								

Table 5 compares the clinical data from the beginning of treatment of the 14 patients and the first NCS of 8 patients who had had years before the biopsy with the clinical and NCS data before the biopsy of the 14 patients. Clinical and electrophysiological worsening of the total number of affected nerves was observed, even though the data for years before the biopsy is not available for all patients.

Table 5

Clinical electrophysiological comparison of each altered nerve years before and by the time of biopsy

Clinical impairment				NCS		
Nerve						
First evaluation						
Sensory	T/P	Tactile	MI	sNCS	MI	
Median	7/26 (26%)	6/28 (21.4%)	2/28	9/16 (56.2%)	12/28	
Radial	7/26 (26%)	7/28 (25%)	2/28	4/16 (25%)	12/28	
Ulnar	9/26 (34.6%)	8/28 (28.6%)	2/28	9/16 (56.2%)	12/28	
Sural	20/26 (76.9%)	18/28 (64.3%)	2/28	16/16 (100%)	12/28	
Superficial peroneal	17/26 (65.4%)	11/28 (39.3%)	2/28	2/2 (100%)	26/28	
Motor			VMT	MI	mNCS	MI
Median			0/24 (0%)	0	6/16 (37.5%)	12/28
Ulnar			3/24 (12.5%)	0	12/16 (75%)	12/28
Common peroneal			4/24 (16.6%)	0	7/16 (43.7%)	12/28
Tibial			2/24 (8.3%)	0	0/2 (0%)	26/28
By the time of biopsy						
Sensory	T/P	Tactile	MI	sNCS	MI	
Median	12/24 (50%)	9/26 (34.6%)	4/28	24/28 (85.7%)	0/28	
Radial	11/24 (45.8%)	8/26 (30.8%)	4/28	20/28 (71.4%)	0/28	
Ulnar	17/24 (70.8%)	9/26 (34.6%)	4/28	23/28 (82.1%)	0/28	
Sural	22/24 (91.6%)	20/26 (76.9%)	4/28	26/28 (92.5%)	0/28	
Superficial peroneal	21/24 (87.5%)	18/26 (69.2%)	4/28	18/18 (100%)	0/28	

Clinical impairment	NCS			
	VMT	MI	mNCS	
<b>Motor</b>				
Median	0/22 (0%)	6/28	19/28 (67.8%)	0/14
Ulnar	6/22 (27.3%)	6/28	23/28 (82.1%)	0/14
Common peroneal	4/22 (18.2%)	6/28	17/28 (60.7%)	0/14
Tibial	0/22 (0%)	6/28	8/16 (50%)	12/28
MI = Missing information; T/P = Thermal and Painful sensitivity; VMT = Voluntary Motor test; sNCS = sensory NCS; mNCS = motor NCS				

**LL patients presented worsened neurological symptoms irrespective of the use of prednisone or thalidomide.**

In the period between the beginning of the treatment and the nerve biopsy, patients were followed up and treatment of leprosy and reactions were evaluated. During all the years of follow-up, during and after the end of MDT, patients used corticosteroids and / or thalidomide to treat neuropathic pain, which was refractory to the withdrawal of these medications. They had received a total dosage of 315.31 grams, with an average of 24.25 grams of prednisone (2.32 to 44.03 grams) and a total dosage of 1352.34 grams, with an average of 104.02 grams of thalidomide (0 to 297.4 grams) (Figure 1). During this time, patients were treated as if they had chronic neuritis, but there was a worsening of symptoms despite treatment or only a relief of symptoms that worsened following the attempt to withdraw medication. Deterioration of electrophysiological findings was also found, and, therefore, nerve biopsy was indicated for better evaluation of the condition.

All patients had inflammatory infiltrate and 13 (92.9%) of them were positive for acid-fast bacilli. Eleven (78.57%) patients were submitted to a new cycle of MDT treatment since they presented clinical and neurophysiological worsening and were unresponsiveness to corticosteroids.

## Discussion

Early diagnosis of leprosy and adequate therapeutic coverage reaching all diagnosed individuals are priorities in a leprosy control program and essential conditions for the interruption of transmission and the reduction of the physical and social consequences of the disease<sup>15</sup>, however, our data showed that this group of patients evolved with neurological worsening despite permanent neurological surveillance and treatment with corticosteroids.

This group of patients demonstrated extensive nerve damage in the absence of symptoms at the beginning of the disease. Vital and colleagues (2012) reported that nerve damage in patients with multibacillary leprosy might occur without symptoms from the onset of the disease<sup>5</sup>. Our data corroborate these findings, as well as Rambukkana's study (2004), which described that neurological abnormalities in leprosy occur early in a slowly progressive manner, even before dermatological lesions occur<sup>16</sup>.

MB patients evolve with more extensive neurological involvement, usually without pain and a slower progressive evolution, with characteristics of neurodegeneration or silent neuropathy<sup>1</sup>. Nerve involvement by *M. leprae* occurs even without the inflammatory process either early or during the course of the disease when the bacillus promotes Schwann Cell (SC) parasitism and alters nerve function through mechanisms that need to be clarified. This condition of sensory or sensory-motor nerve dysfunction that occurs without pain and evolves indolently, often gone unnoticed by the patient, is called silent neuritis or silent neuropathy<sup>17,18</sup>. Medeiros and colleagues (2016) described profound modulation of SC metabolism during *M. leprae* infection and hypothesized that lactate reduction in SCs could be behind a new mechanism of demyelination and neuronal death in leprosy neuropathy<sup>19</sup>.

Our series revealed that pain was an unusual symptom at the onset of treatment and there was a significant increase in persistent spontaneous pain, without the classic features of acute neuritis, following MDT treatment, leading us to believe that it was chronic neuropathic pain.

The presence of nerve thickening, as well as the disability index, did not prove to be good criteria for assessing follow up of peripheral neuropathy in these patients. Thickening of nerve trunks persisted in more than half of cases, especially MB ones, even 5 years after the end of treatment (RFT), and continued for longer than skin lesions, according to Porichha and colleagues study (2011)<sup>20</sup>. WHO functional disability grade scale is used to assess and monitor patients' "disabilities" during treatment and includes changes in the eyes, hands and feet<sup>10</sup>. However, it does not seem to be a good method for monitoring their neurological damage. In this group of patients, there was an improvement in the degree of disability despite the demonstration of worsening from a clinical and neurophysiological point of view.

Furthermore, we observed a progression of clinical and electrophysiological changes in the peripheral nerve, with a predominantly sensory onset and progressive compromise in the number of increasingly larger fibers, as occurs in degenerative diseases of the peripheral nervous system, well described by Ooi and Srinivasan (2004)<sup>1</sup>. Rambukkana (2002) proposed that *M. leprae* propagates a nonmyelinating phenotype by inducing demyelination and nerve injury in myelinated Schwann cells in the early phase of infection, possibly explaining the sensitive predominance of peripheral neuropathy<sup>21</sup>.

In our patients, nerve damage responded poorly to long treatments with high doses of corticosteroids and / or thalidomide. While studying borderline patients, Rosemberg and colleagues (2003) found a poor response to corticosteroids in all patients, where the response was incomplete<sup>22</sup>.

## Conclusions

LL patients can develop progressive degenerative peripheral neuropathy from disease onset and nerve damage continues to evolve despite multiple year treatment with high doses of corticosteroids.

Further studies are needed to elucidate this continuous worsening of peripheral neuropathy in lepomatous patients, in order to initiate clinical trials for new drugs that may prevent the progression of peripheral nerve damage in these patients.

This group of patients is a small percentage of the LL patients followed up in our service, but for whom we had all the information for clinical evaluation of the objectives of this work. Thus, the evolution of peripheral neuropathy in these cases does not necessarily represent the natural history of the disease in LL patients.

To better assess this outcome, our group is developing a prospective research project to assess peripheral neuropathy from the beginning of treatment and throughout the follow-up process at the institution.

## Declarations

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### Authors Contributions:

Conceived the study: PSP, MRJ. Performed the review of medical records: PSP, AMS. Analyzed the data: MH. Wrote the paper: PSP. Performed clinical evaluation: AMS. Performed neurological and electrophysiological testing: RTV, IJRP, MRJ. Performed biopsy analysis: SLGA, ENS. Performed several edits of the draft manuscript: ROP, MRJ, PSP. Supervised neurological testing and contributed to the writing of the paper: MRJ.

### Conflicting interests:

All the authors declare that have no conflicting interests.

**Ethics Statements:** The research was carried out in compliance with the International Norms on Ethics in Human Research, having been previously approved by the Ethics Committee of the Oswaldo Cruz Foundation (Approval number: 3.152.162). All patients voluntarily provided their written informed consent.

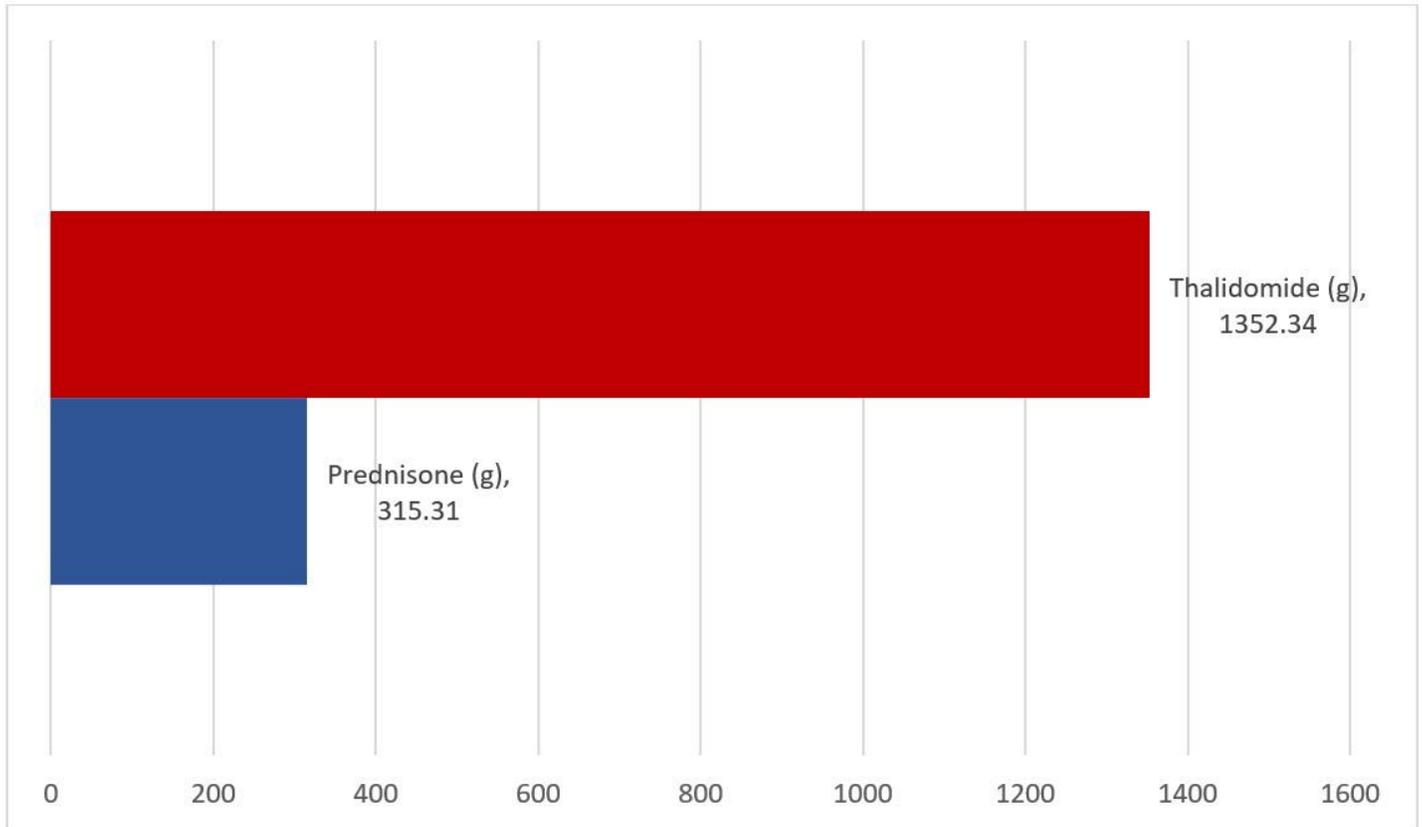
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## Figures



**Figure 1**

Total dosage of medication taken throughout the years