

# Clinical and electrophysiological characteristics of neuropathic pain in leprosy patients: A prospective cross-sectional study

Danusa Neves Somensi, Emanuel de Jesus Soares de Sousa<sup>1</sup>, Geovanna Lemos Lopes, Gustavo Celeira de Sousa<sup>1</sup>, Marília Brasil Xavier

Department of Dermatology, Federal University of Para, <sup>1</sup>Department of Specialized Health, Para State University, Belém, Pará, Brazil.

## Abstract

**Introduction:** Neuropathic pain is a common and disabling late complication of leprosy. We investigated the clinical and electrophysiological characteristics of neuropathic pain in leprosy patients by evaluating nerve conduction, sympathetic skin response (SSR) and A-waves.

**Methods:** Twenty one leprosy patients with neuropathic pain validated by the *Douleur Neuropathique en 4 (DN4) Questionnaire* were selected for study. Pain intensity was measured by the visual analog scale. Demographic and clinical data were collected for all patients. Clinical data included appraisal of the median, ulnar, radial, tibial and common peroneal nerves, assessment of the sympathetic skin response and conventional electrophysiological recordings.

**Results:** Among all electroneuromyographic presentations, multifocal mononeuropathy was still the most prevalent. Sensory loss was observed more frequently than motor deficits. As most patients presented advanced clinical forms of leprosy and were under treatment, this high mean was found and the ulnar nerve was most frequently affected. The sympathetic skin response was absent in 16 patients. Higher DN4 Questionnaire scores were observed in women and in those receiving corticosteroid therapy. These inferences are possible to be made, but our study's limitations don't allow us to be certain about it. The statistical significance found only permits us to evidence what we related on the textual part of the study.

**Limitations:** The small number of patients studied, the lack of sophisticated diagnostic methods for leprosy, as well as the difficulties in assessing nerve conduction were the main limitations of this study.

**Conclusion:** The neurophysiological and clinical findings in leprosy neuropathy were modest despite the conspicuous neuropathic pain. Although electrophysiological studies are a vital tool to verify nerve damage, variations in the clinical presentation of leprosy neuropathic pain render the diagnosis challenging. Further studies are needed to describe the neurophysiological evolution of this disease.

**Key words:** Electroneuromyography, electrophysiology, leprosy, neuropathic pain, neuropathy

## Introduction

Leprosy is a common, treatable cause of peripheral neuropathy in many tropical and subtropical countries.<sup>1,2</sup> *Mycobacterium leprae* has a distinct predilection for areas of low body temperature and a unique tropism for nerves. It frequently afflicts the ulnar nerve possibly due to its superficial location. The frequent delays in the diagnosis of leprosy allows the progression of nerve damage, often resulting in deformity.<sup>1,3-5</sup>

Neuropathic pain is a common symptom afflicting over 60% of patients with leprosy and may present before, during,

or after treatment. It is frequently reported during leprosy reactions.<sup>6</sup> The International Association for the Study of Pain defines neuropathic pain as “pain initiated or caused by a primary lesion or dysfunction in the nervous system.”<sup>6-9</sup> Neuropathic pain originating in the peripheral nervous system as occurs in leprosy is characterized by injury to thin and nonmyelinated fibers. This type of injury is difficult to assess by conventional neurophysiological techniques such as electroneuromyography, although late latency evaluations such as the F-wave and sympathetic skin response are useful in their detection.<sup>1</sup> Even in the absence of distal alterations,

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**Corresponding author:** Prof. Gustavo Celeira de Sousa, Bernal do Couto Ave., 1003, Belém, Pará, 66055-080, Brazil. [gustavo.c.sousa0@gmail.com](mailto:gustavo.c.sousa0@gmail.com)

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the A-wave tends to appear during the F-wave study in patients complaining of neuropathic pain.<sup>1,10,11</sup>

The previous studies have suggested that neuronal dysfunction occurs long before the clinical deterioration and the involvement of the nerve trunks.<sup>12-15</sup> We conducted a systematic electrophysiological evaluation of leprosy patients with neuropathic pain, to correlate the clinical and electrophysiological findings.

## Methods

### Study design

We enrolled 21 leprosy patients with neuropathic pain from January to November 2014 from two reference centers for monitoring leprosy in Belém (Pará, Brazil): *Centro Saúde Escola do Marco* and *Núcleo de Medicina Tropical*. The study was approved in *Universidade do Estado do Pará's* (UEPA) Ethics Committee on Human Research (CAAE) (Document No: 34662414.0.0000.5174).

### Inclusion and exclusion criteria

Leprosy patients with neuropathic pain defined by the evaluation of the DN4 questionnaire were selected for the study. All patients were over 18 years of age and gave written consent. Patients at risk for other causes of neuropathy such as diabetes, alcoholism, HIV infection, or a family history of hereditary neuropathy were excluded from the study. The presence of acid-fast bacilli was not a criterion due to its low sensitivity for the diagnosis of leprosy.

### Clinical evaluation

The diagnosis of leprosy in all study participants was made by a physician after clinical evaluation and examination of slit skin smears from both ear lobules for AFB. All patients were categorized based on the main clinical presentation as paucibacillary or multibacillary.<sup>14</sup> The neuropathic pain was evaluated by a neurologist using both clinical criteria and the *DN4 Questionnaire* (score >4).<sup>8</sup> All patients were then subjected to a clinical and electrophysiological evaluation.

Patients were classified as having neuropathic pain based on the grading system elaborated by Treede *et al.*<sup>8</sup> A simplified neurological assessment was then conducted by a physiotherapist using Semmes-Weinstein monofilaments and a manual muscle-strength assessment was performed. The disability grade was evaluated according to *Ministério da Saúde's* guidelines.<sup>16-18</sup>

### Neurophysiological evaluation

The neurophysiological assessment was performed with a Neuropack MEB-9200, 4-channel EP/electroneuromyography system (Nihon Kohden, Tokyo, Japan) using the protocol detailed by Garbino *et al.*<sup>1</sup> The sympathetic skin response was recorded with the low-frequency filter at 0.5 Hz, the high-frequency filter at 5000 Hz and sweep set at 5s. A single stimulus of 10–15 mA of 0.2 ms duration was delivered with a cathode placed proximally on the median and posterior tibial nerves. The recording electrodes were placed on both hands and feet (palmar, plantar as well as dorsal surfaces of hands and feet). Non-recordable responses were noted as abnormal.

### Statistical analysis

The sample size was influenced by the difficulty in recruiting patients. The data were structured in a Microsoft Excel 2013 database and a BioEstat 5.0 program (Instituto Mamirauá, Tefé, Manaus, Brazil). The GraphPad Prism (GraphPad Software, San Diego, CA) was used for the generation of statistical results. The association of variables was assessed using the mean, median and standard deviation values, followed by the t-test and/or Pearson's linear correlation. Confidence intervals (95%) and significance levels ( $\alpha = 5\%$ ;  $P \leq 0.05$ ) were established.

### Results

Mononeuropathy or multiple mononeuropathy patterns were most frequently seen [Table 1]. The A-wave was infrequent (5/21) in the nerve conduction studies (19%). There was significant difference between those with mononeuropathy/ multiple mononeuropathy and the others (Chi-square,  $P = 0.0088$ ). The sympathetic skin response was absent in 16 patients – on the soles in ten patients, on the palm in one patient and on both palms and soles in five patients [Figure 1]. The superficial fibular nerve was the most affected, followed by the sural nerve. In our study, some patients with thickened nerves had normal nerve conduction studies.

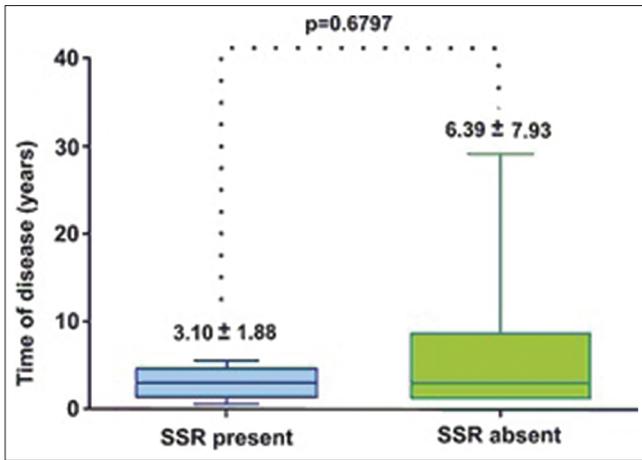
Of the 21 enrolled patients, 13 were men and eight were women. The average age of the patients was  $41.3 \pm 12.4$  years [Figure 1]. The majority of enrolled patients had multibacillary disease (19/21 patients). Seventeen of the patients had dimorphic leprosy and 11 patients had type I reaction [Table 2]. The duration of disease at presentation ranged from 13 to 72 months in 12 patients and the duration of multidrug therapy ranged from 7 to 12 months in 13 patients [Figure 1]. Seventeen of the 21 patients were on corticosteroid therapy [Tables 3 and 4]. The ulnar nerve was most frequently affected and 18 patients exhibited some degree of disability [Table 2].

### Discussion

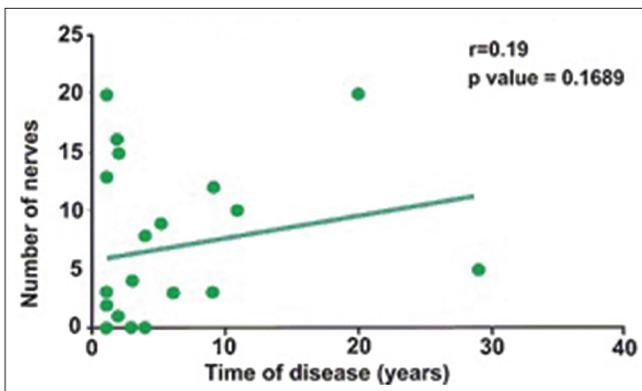
Neuropathic pain is a frequently overlooked symptom in the management of leprosy. Patients during or after multidrug therapy have a high prevalence of neuropathic pain.<sup>10,19-22</sup> Although the frequency and nature of the neuropathic pain in leprosy is unclear, it seems that late diagnosis of leprosy and the evolution of nerve damage contributes to the onset of

**Table 1: Distribution of 21 patients with leprosy according to electromyographic pattern**

Electroneuromyography patterns	n (%)
Mononeuropathy/multiple mononeuropathy	5 (23.8)
Asymmetric sensorimotor neuropathy with focal slowing	4 (19.0)
Asymmetric sensory neuropathy	2 (9.5)
Asymmetric axonal sensorimotor neuropathy	1 (4.8)
Symmetrical axonal sensorimotor neuropathy	1 (4.8)
Others	4 (19.0)
Normal	4 (19.0)
Total	21 (100.0)



**Figure 1a:** Relationship between disease duration and sympathetic skin response of the 21 patients in the study



**Figure 1b:** Pearson correlation coefficient of affected nerves according to electroneuromyography and disease duration of the studied sample. Tropical Medicine Center, HCSM-UEPA—Belém-PA, 2014

**Table 2: Relationship between the clinical characteristics of patients with neuropathic pain and electroneuromyography findings (n=21)/Belém PA, 2014**

Clinical characteristics	EMG, n (%)		t TEST DN4 P-value
	Changed	Normal	
Clinical form			
Mutibacillar	16 (94.1)	3 (75)	0.8271
Paucibacillar	1 (5.9)	1 (25)	
Leprosy reaction			
With reaction	9 (52.9)	2 (50)	0.6507
Without reaction	8 (47.1)	2 (50)	
Grade of disability			
Grade 0/I	8 (47.1)	4 (100)	0.1472
Grade II	9 (52.9)	0 (0)	

EMG: Electroneuromyography

pain [Table 3] Neuropathic pain is most commonly seen in borderline and MB cases.<sup>10,23-26</sup>

Multifocal mononeuropathies are the most prevalent neurophysiological pattern and the ulnar nerve is most often affected.<sup>27,28</sup> Electromyography is an excellent tool

**Table 3: DN4 scores with demographic, clinical and electrophysiological variables of patients with neuropathic pain (n=21)/Belém-PA, 2014**

Variables	Mean	Median	SD	VAS	P-value
Sex					
Female	8.38	9	0.88	0.0359*	
Male	7.17	7	1.27		
Age					
<45	7.5	8	1.2	0.82	
>45	7.9	7	1.1		
Corticosteroid					
Yes	8	8	0.9	0.0009*	
No	6	6	0.7		
Sympathetic skin response					
Present	8	7.8	1.2	0.7726	
Absent	7.5	7.6	1.2		
Reaction					
Yes	8.1	8	1.22	0.1004	
No	7.2	7	1.13		
Grade of disability					
Grade 0/I	7.7	8	1.2	0.1593	
Grade II	7.7	8	1.2		

\*Student's t-test/P<0.05. SD: Standard deviation, VAS: Visual analog scale

**Table 4: Visual analog scale scores with demographic, clinical and electrophysiological variables of patients with neuropathic pain (n=21)/Belém-PA, 2014**

Variables	Mean	Median	SD	P-value
Sex				
Female	8	9	1.7	0.0822
Male	6.8	7	1.3	
Age				
<45	7.1	7.5	1.5	0.8914
>45	7.3	7.5	1.5	
Corticosteroids				
Yes	7.5	7.5	1.5	0.2873
No	6.3	6.5	1.8	
SSD				
Present	8	9	1.5	0.164
Absent	7.1	7	1.5	
Reaction				
Yes	7.7	8	1.4	0.2453
No	5	7.5	1.6	
Grade of disability				
Grade 0/I	7.3	7.5	1.8	0.2008
Grade II	6.7	7.5	2	

\*Student's t-test/P<0.05. SD: Standard deviation, SSR: Sympathetic Skin Response

for early detection and monitoring nerve damage.<sup>2,29-31</sup> In our study, some patients with thickened nerves had normal nerve conduction studies. This clinicoelectrophysiological dissociation may be due to the involvement of few fascicles initially sparing of the faster conducting fibers.<sup>32-34</sup> Contrary to the findings of Garbino *et al.*, we found a low prevalence

of A-waves which may be due the fact that most patients had been treated or were under treatment with corticosteroids [Table 4].<sup>35-36</sup>

### Limitations

Neuropathic pain is a subjective symptom and it was difficult to characterize and evaluate. Many patients refused consent when the electromyography procedure was explained which may result in bias. Patients often arrived late in the course of the disease, or with unknown comorbidities causing pain of nociceptive nature. Thus, further studies are needed to validate the findings of this study and overcome these limitations.

### Conclusion

In this study, mononeuropathy and multiple mononeuropathy were the most common patterns and the ulnar nerve was the most affected nerve trunk. The neurophysiological assessment did not reveal the predominance of any specific electromyographic pattern and some patients in this study showed normal nerve conduction studies. The DN4 questionnaire scale revealed more intense pain in female patients and in patients on corticosteroids.

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### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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