

## Clinical and Neurophysiological Features of Leprosy Patients with Neuropathic Pain

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**Abstract.** Neural pain is a frequent symptom in leprosy disease. There is a paucity of data regarding neural pain diagnostics resulting in common prescriptive errors when neuritis is confused with neuropathic or mixed nociceptive–neuropathic pain. The present study identified important demographic, clinical, and neurophysiological features of 42 leprosy neuropathy patients presenting neuropathic pain (NP). During routine evaluations, patients were selected asking if they had ever experienced neural pain. Data analyses of their pain characteristics, clinical examination results, and both the Douleur Neuropathique 4 Questionnaire and Hamilton Depression Scale scores were used to classify these patients. The most common word they used to describe the sensation of pain for 25 (60%) of these patients was “burning.” In the early stages of the disease and before leprosy diagnosis, 19 (45%) had already complained about NP and leprosy treatment was unable to prevent its occurrence in 15 (36%). Leprosy reactions, considered NP risk factors, occurred in 32 (76%) cases. Knowledge of typical NP characteristics could be used to develop more effective therapeutic approaches for a notoriously difficult-to-treat pain condition.

### INTRODUCTION

Despite widespread implementation of effective multidrug therapy (MDT), leprosy has not been eliminated. In spite of treatment, a third of newly diagnosed patients have nerve damage and might later develop disabilities and delayed nerve impairment.<sup>1</sup> Moreover, different types of pain related to nerve injury may occur during the course of the disease, contributing to patient morbidity.

In leprosy, a variety of physiopathological mechanisms are directly related to neural pain. Nociceptive pain is initiated by a noxious stimulus such as neuritis, an inflammatory process affecting the nerves. Neuritis differs from neuropathic pain (NP), a nonexclusive condition of leprosy that occurs in abnormal functioning of the peripheral and central nervous systems in several associated etiologies (e.g., cancer, diabetes, and herpes zoster).<sup>2–4</sup> It is common for neuritis to be associated with certain features of NP, making it difficult to reach correct differential diagnostic and to decide the best treatment.<sup>5</sup>

During neuritis, deterioration of the nerve function associated with pain usually recovers after administration of oral steroids.<sup>6</sup> On the other hand, NP relief most often occurs as a result of tricyclic antidepressives, dual reuptake inhibitors of serotonin and norepinephrine, anticonvulsivant drugs, and topical anesthetics.

The present cross-sectional study aimed to achieve a more thorough understanding of NP in leprosy and identify its characteristics to improve differential diagnosis and treatment. Demographic and clinical features in confirmed leprosy patients with NP are described. It is hoped that knowledge of these findings will guide health professionals in pain management and aid in building tools to accurately diagnose leprosy-related pain.

### METHODS

**Subjects.** The present study was carried out at the Leprosy Outpatient Clinic, Oswaldo Cruz Foundation, Rio de Janeiro, RJ, Brazil, from January 2010 thru May 2013. One hundred and thirty-eight diagnosed leprosy patients with NP were recruited during a routine visit, 93 of whom were excluded. The exclusion criteria were associated with other NP etiologies than leprosy, namely, diabetes, alcoholism, the human immunodeficiency virus infection, rheumatological diseases, and toxic neuropathy in addition to hepatic and/or renal diseases. Furthermore, patients with pain syndromes such as acute neuritis, complex regional syndromes, fibromyalgia, pain ulcerations, radiculopathy, joint pain, and tendonitis and those who had been treated for NP within the previous 6-month period and could not remember any pain characteristics were excluded. Eligibility criteria included being 18 years of age or older, fluency in the Portuguese language, and the ability to understand questions during anamnesis.

**Clinical history and questionnaires.** Patient information including gender, age, educational level, leprosy characteristics, and previous leprosy reactions were recorded. Participants were asked to describe their pain in words such as shooting, electric shock-like, burning, prickling, and tingling as well as the onset, duration, location, and any possible trigger factors (e.g., whether the pain began spontaneously, during cold or hot weather, as a result of strenuous effort, or simply touching). Patients also reported on factors that led to lessening of pain (rest, movement, friction, limb elevation, and a heating pad) together with subjective effects as a result of pain (nausea, insomnia, irritability, lack of concentration, anger, death wishes, tearfulness, decreasing interest in physical activity, and change of appetite). Patients were likewise tested to determine pain intensity using the Visual Analog Scale (VAS-INT) from 0-to-absent and 10-to-worst imaginable pain. Patients answered the validated Portuguese Douleur Neuropathique 4 (DN4) scale and the Hamilton Depression Rating Scale (HAMD) to assess depressive symptoms.<sup>7–9</sup> In the HAMD, depression was considered absent when the final score was 0–7, mild when it was 8–16, moderate in the case of 17–23, and severe when it was  $\geq 24$ .<sup>10</sup>

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**Clinical examination.** Neurological evaluations focusing on the peripheral nerves were performed. Enlargement of the main leprosy-affected peripheral nerves (the greater auricular, ulnar, radial cutaneous, lateral popliteal, and posterior tibial nerves) were appraised. Palms and soles were examined for the presence of cyanosis. Pain and thermal sensitivities were tested by a safety pin and cold materials (15°C cold), respectively. Tactile sensitivity was tested using Semmes-Weinstein monofilaments.<sup>11</sup> The normal threshold was set at a monofilaments feeling of 200 mg in the hand and 2 g in the foot.<sup>11,12</sup> Assessments were made of innervated areas by way of the trigeminal, ulnar, median, radial, sural, superficial fibular, and plantar nerves. Both hypoesthesia and anesthesia were considered abnormal. Sensitivity impairment was graded as mild when only pain sensitivity was abnormal; moderate when pain and thermal sensitivities were abnormal; and severe if abnormal tactile, pain, and thermal sensitivities in any of the tested nerve areas were detected. Individual muscle strength in the upper and lower extremities was determined by the Medical Research Council (MRC) scale.<sup>13</sup> Motor impairment was diagnosed if the MRC scale of any muscle was  $\leq 4$  on the 0–5 rating. Tendon reflexes were tested using a Taylor's hammer. Disability was recorded in accordance with the standard World Health Organization grading criteria and allodynia was assessed by applying a light brush in the painful area.<sup>14</sup>

**Electrophysiological examination.** Nerve conduction was only verified in painful limbs. Parameters were measured by way of the Neuropack  $\mu$ MEB 9100 EP/EMG measuring system (Nihon Kohden Corp., Tokyo, Japan) in all patients. Skin temperatures were taken at the wrists and ankles and maintained above 33°C whereas room temperatures ranged between 29 and 32°C. Standard methods were performed according to Delisa, 1994.<sup>15</sup> Sensory nerve conduction studies included the radial, median, ulnar, sural, and superficial fibular sensory nerves whereas motor nerve conduction studies included the ulnar, median, tibial, and common peroneal nerves.

**Case definitions.** Neuropathic pain was assessed on the basis of pain history and the physical examination results. Pain in the same areas and with the same distribution of negative or positive sensory signs (i.e., hypoesthesia, hyperesthesia, hypoalgesia, hyperalgesia, or allodynia) was adopted as a diagnostic criterion for NP in leprosy neuropathy patients.

**Ethical considerations.** Our research was carried out in compliance with the International Norms on Ethics in Human Research after prior approval by the Ethics Committee of the Oswaldo Cruz Foundation.

**Analysis.** The sensitivity and specificity of the DN4 were calculated using  $2 \times 2$  tables. The clinical diagnostic results were considered the gold standard.

TABLE 1  
Demographic characteristics and clinical features of 42 leprosy patients with neuropathic pain

Demographic characteristics and clinical features	Patients	
Gender	F M	18 (43%) 24 (57%)
Age	Median (Min–Max)	47.5 (20–74)
Years of schooling	NI AA < 4 years 4–7 years > 7 years	3 (7%) 6 (14%) 16 (38%) 9 (21%) 8 (19%)
Grade of disability	NI 0 1 2	5 (12%) 12 (29%) 17 (40%) 8 (19%)
Ridley and Jopling clinical classification scale	TT BT BB BL LL Indeterminate Pure neuritic leprosy	1 (2%) 1 (2%) 5 (12%) 10 (24%) 19 (45%) 1 (2%) 5 (12%)
WHO classification	PB MB	7 (17%) 35 (83%)
DN4 score	< 4/10 $\geq 4/10$	3/40 37/40
Hamilton depression scale score	NI Absent Mild Moderate Severe	5 (12%) 8 (19%) 16 (38%) 6 (14%) 7 (17%)
Severity of pain	Mild Moderate Severe	0 17 (40%) 25 (60%)
Relationship between onset of pain and the beginning of MDT	Before MDT During MDT After MDT	19 (45%) 8 (19%) 15 (36%)
Previous leprosy reaction		32 (76%)

AA = illiterate and literate; BB = mid-borderline; BL = borderline-lepromatous; BT = borderline-tuberculoid; DN4 = douleur neuropathique 4; F = female; LL = lepromatous; M = male; Max = maximum; MB = multibacillary; MDT = multidrug therapy; Min = minimum; NI = not informed; PB = paucibacillary; TT = tuberculoid.

RESULTS

The present study included 42 diagnosed leprosy patients, 24 (57%) of whom were males. The mean age was 47.5 (ranging from 20 to 74) and 35 (83%) had MB leprosy. Forty percent of the patients had a WHO grade 1 disability and seven (16%) were relapse cases. Additional data are presented in Table 1.

Previous reactions in leprosy before evaluation occurred in 32 patients (76%). Twenty-three (55%) of these patients had previously more than one type of reaction. Previous neuritis occurred in 50% of 32 patients, as erythema nodosum leprosum. Erythema multiforme occurred in 19 (59%) and reversal reaction in 12 (38%). Nine of them had had the first acute neuritis before starting NP.

Pain started before treatment in 19 (45%) patients and after MDT in 15 (36%). The mean VAS-INT was 7.82 (range 3–10). “Burning” was the most commonly cited word to describe pain. Twenty-five (60%) patients referred to a burning sensation, 17% said it was electric shock-like, 9% described it as a shooting pain, 7% as prickling, and the remaining 7% as tingling. Features related to NP are listed in Table 2.

Motor impairment was present in 17 patients (40%) and all suffered some degree of sensory impairment. More than 60% had one or more enlarged nerves and 14% had nerve tenderness on palpation (Table 3).

**Nerve conduction studies.** Fourteen (33%) patients showed no alterations in any of the nerves evaluated in the painful limb as a result of the nerve conduction study. Among the 67% with altered sensory nerve conduction, all had at least one nerve with no identifiable conduction, but most were found to have an axonal commitment pattern.

DISCUSSION

Despite the existence of criteria defining NP, recognizing the different frames of NP and neuritis remains a challenge, resulting in common prescriptive errors whenever neuritis is mistaken for NP or mixed nociceptive–neuropathic pain or

TABLE 2

Subjective pain characteristics of 42 leprosy patients with neuropathic pain

Subjective pain characteristics		Patients
Spontaneous pain		31 (74%)
Trigger factors	Cold weather	10 (24%)
	Hot weather	4 (10%)
	Touching	6 (14%)
	Effort	21 (50%)
Improvement factors	Resting	19 (45%)
	Movement	9 (21%)
	Limb elevation	10 (24%)
	Localized friction	9 (21%)
	Localized heating	5 (12%)
Subjective effects	Nausea	5 (12%)
	Insomnia	20 (47%)
	Irritability	21 (50%)
	Lack of concentration	20 (47%)
	Anger	13 (31%)
	Death wish	3 (7%)
	Tearfulness	8 (19%)
Decreased physical activity		19 (45%)
Appetite	Decreased	4 (10%)
	Increased	6 (14%)

TABLE 3

Clinical results of 42 leprosy patients with neuropathic pain

Clinical signs during neurological examination		Patients
Sensory impairment	Mild	6 (15%)
	Moderate	17 (40%)
	Severe	19 (45%)
Paraesthesia		32 (76%)
Allodynia		5 (12%)
Palmar or plantar erythrocyanosis		12 (29%)
Thickened nerves		25 (60%)
Motor Impairment		17 (40%)

vice-versa. Again, the present study describes relevant NP features in leprosy that are useful for obtaining a complete clinical evaluation.

The occurrence of NP in leprosy has been comprehensively reviewed. The resulting data can range anywhere from 17% to 70.3% among all neuropathy leprosy patients according to both Haroun et al.<sup>16</sup> and Ramos et al.<sup>17</sup>, respectively. In our Leprosy Outpatient Clinic, the estimation is 15%. There are presently available tools capable of identifying NP. One is The Leeds Assessment of Neuropathic Symptoms and Signs developed in the United Kingdom; another is the DN4 Questions developed in France. Three studies have used the DN4 questionnaire and found different prevalence rates: 11.2%, 21.8%, and 78.9%.<sup>16,18,19</sup> The DN4 in the present study showed a 93% sensitivity rate whereas Haroun et al.<sup>16</sup> obtained a full 100%. Douleur Neuropathique 4 is a reliable screening tool to identify patients with possible NP. Its use should be encouraged, particularly by non-neurologists. Although not seem specific for diagnosis of NP and has shown 45% of specificity, its use is convenient and practical, making it an attractive tool in treating the leprosy patients who have neuritis or NP despite MDT.<sup>16</sup> As several authors have suggested, MDT does not appear to prevent the occurrence of NP or even interrupt the development of neuropathy. Patients may suffer NP despite bacillary elimination at the end of the treatment.<sup>20–23</sup> Because of low DN4 specificity, the present authors are developing a questionnaire that could prove useful in the differential diagnosis of neuritis and NP.

Whereas chronic pain is more prevalent among the female population, leprosy infection and NP are more common among adult males.<sup>24,25</sup> These findings clearly indicate the high risk of impoverishment within stricken families considering that the economically active population is most severely affected by leprosy and NP.<sup>20–22,26</sup>

Beyond pain, other psychological comorbidities such as depression, anxiety, and sleep disorders increase the suffering. Our study identified insomnia in almost half of all patients, albeit significantly less than the 94% found in a Chinese study on leprosy.<sup>20</sup> The same problem exists in 72.2% of diabetic patients with painful neuropathy and 69.7% of those with postherpetic neuralgia.<sup>27</sup> Using the Hamilton Depression Scale, depression is close to 70% or less in leprosy patients with NP, similar in 72.1% painful diabetic neuropathy, and 77.8% in postherpetic neuralgia patients.<sup>27</sup> However, our finding could be even higher because 12% of our patients were not given a HAMD test. Indeed, all our findings emphasize the importance of including the evaluation of quality of life, sleep disorders, and signs of depression in patients with chronic pain.

Previous studies have reported on patients describing their pain as a burning sensation (thermal symptoms), tingling, pins and needles, pricking, cutting, lacerating (dysesthetic symptoms), electric shock-like, and jumping-bursting (paroxysmal symptoms), all of which were significantly more common in NP than in nociceptive pain. In the latter, dull, aching, and throbbing sensations were more common.<sup>28</sup> Taking into account the ethnical background and language of Brazilian patients, “burning” seems to most often describe NP in this country, as was seen in the present study. Previous research in Bangladesh, India, and Ethiopia, for example, have shown similar statistics.<sup>16,21,29</sup>

As neurological impairment, leprosy reactions are considered risk factors to NP and occurred in 32 (76%) cases.<sup>17,22</sup> Even more prevalent in our evaluation, a history of type 2 reactions also showed a significant association.<sup>20,22</sup> Previous studies have found that neural thickening takes place from 45.5% to more than 90% of all cases, which is comparable to the 60% found in the present study.<sup>16,18</sup> Furthermore, the prevalence of sensory impairment was higher than the incidence of motor dysfunction, likewise in conformity with other studies on leprosy patients overall.<sup>30,31</sup> Pain triggered by touch raises the possibility of an inflammatory component in the pathophysiological process of pain, as would naturally be expected in neuritis due to local inflammation. This same finding was perceived by 14% of patients, less than 30% in previous studies.<sup>16</sup> Our study excluded patients with nerve pain during episodes of neuritis. Of course, it was assumed that at least some of these patients could be experiencing NP associated with neuritis. But because of the difficulties involved in dissociating the two types of pain, it was decided not to include them in this work.

It is known that NP can occur without an obvious neurological impairment, as in small-fiber neuropathies. In this connection, normal neural conduction was identified in 14 (33%) patients, reinforcing the integrity of large diameter fibers. Whereas large fibers are affected in a relatively late stage of infection, small unmyelinated and lightly myelinated nerve fibers (the C and A $\delta$  nerve fibers) are particularly vulnerable to early damage from *Mycobacterium leprae*.<sup>32-34</sup> NP is more prevalent in neuropathies associated with the prominent involvement of C and A $\delta$  nerve fibers. However, it is not unusual to find NP in patients with mixed large-fiber and small-fiber neuropathies and even in those with predominantly large-fiber involvement.<sup>35</sup> Although the standard nerve conduction study does not provide information on small-fiber function, guidelines recommend as the most useful tool to document and assess peripheral neuropathies.<sup>36</sup>

Quantitative sensory testing (QST) is a psychophysiological measurement of perception in response to external stimuli of controlled intensity. It is used for the diagnosis and follow-up of small-fiber neuropathy. Its usefulness has been confirmed in the early diagnosis of leprosy and in quantifying positive sensory phenomena such as mechanical and thermal allodynia and hyperalgesia.<sup>36</sup> Understanding NP characteristics in patients with small-fiber neuropathy and its features on QST could identify subsyndromes related to pain in leprosy and contribute to the reformation of current therapeutic strategies. Knowledge of the characteristics of this patient subgroup and appropriate techniques to more objectively detect early nerve function impairment could be helpful for early diagnosis and treatment, and will be a second step in the present study.

Understanding the complications involved in leprosy disease, and especially of neural pain, is essential when planning the treatment and rehabilitation of these patients. NP must be differentiated from painful neuritis. Moreover, the exacerbation of pain during reactional episodes must be examined further to avoid improper or excessive corticosteroid therapy and its side effects altogether, opening the way to more effective pain management.

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