Neuropathic pain in leprosy: symptom profile characterization and comparison with neuropathic pain of other etiologies

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Abstract

Introduction: Previous studies reported a high prevalence of neuropathic pain in leprosy, being especially present in "pharmacologically cured" patients. The presence of neuropathic pain in leprosy poses a supplementary burden in patient’s quality of life, daily activities, and mood.

Objectives: The aim of this study was to assess whether neuropathic pain in leprosy has similar symptom profile as neuropathic pain of other etiologies and to retrospectively assess the efficacy of neuropathic pain medications regularly prescribed to leprosy.

Methods: Leprosy and nonleprosy patients had their neuropathic pain characterized by the neuropathic pain symptom inventory (NPSI, ranges from 0 to 100, with 100 being the maximal neuropathic pain intensity) in a first visit. In a second visit, leprosy patients who had significant pain and received pharmacological treatment in the first evaluation were reassessed (NPSI) and had their pain profile and treatment response further characterized, including information on drugs prescribed for neuropathic pain and their respective pain relief.

Results: The pain characteristics based on NPSI did not significantly differ between leprosy and nonleprosy neuropathic pain patients in visit 1 after correction for multiple analyses, and cluster analyses confirmed these findings (ie, no discrimination between leprosy and nonleprosy groups; Pearson \( \chi^2 = 0.072, P = 0.788 \)). The assessment of pain relief response and the drugs taken by each patient, linear regression analysis showed that amitriptyline, when effective, had the highest percentage of analgesic relief.

Conclusions: Neuropathic pain in leprosy is as heterogeneous as neuropathic pain of other etiologies, further supporting the concept that neuropathic pain is a transetiological entity. Neuropathic pain in leprosy may respond to drugs usually used to control pain of neuropathic profile in general, and amitriptyline may constitute a potential candidate drug for future formal clinical trials aimed at controlling neuropathic pain in leprosy.

Keywords: Neuropathic pain, Leprosy, Candidate drug, Symptom profile, Neuropathy, Symptom

1. Introduction

Leprosy is caused by the infection by Mycobacterium leprae, which currently affects 250,000 new patients annually, mainly affecting economically restricted countries where income is unequally distributed across the population. Because up to 5% of the general population is susceptible to infection by the Mycobacterium, leprosy cases may occur in nonendemic areas, especially in times of high population geographical dislocation. Leprosy is associated with a pleiad of complications, with peripheral neuropathy being one among them. Neuropathic pain occurs in up to 22% of patients and may develop during or after bacteriological cure. In fact, more than 85% of patients with leprosy-related neuropathic pain developed it after the end of the antimicrobial treatment period, constituting a heavy long-term handicap of the disease, and frequently affecting patients who were considered cured and were already discharged from health care. Although several groups have validated screening tools used to detect neuropathic pain in...
leprosy patients, its symptom profile has not so far been compared with neuropathic pain of other etiologies. Additionally, there is, so far, no evidence-based treatment for neuropathic pain in leprosy, which leads to a vicious cycle where leprosy patients have a low propensity of being diagnosed with neuropathic pain, and, when they receive a diagnosis, disinformation on how to conduct the treatment and drug shortage are the rule, in part due to the lack of published data on this issue.

The different forms of leprosy, its evolving clinical phases, and treatment status may all be associated with the occurrence of chronic pain, and leprosy patients present chronic pain in a higher proportion than the general population. Neuropathic pain is also prevalent in leprosy, occurring in 11.2% to 78.9% of patients, and varying according to the setting (eg, field vs referral centers), the timing of assessment (before, during, or after the completion of the antimicrobial treatment), and the clinical presentation of the disease (pauci vs multibacillary). Similar to other etiologies of peripheral neuropathy, the presence of neuropathic pain in leprosy poses a supplementary burden in patient’s quality of life, daily activities, and mood. Neuropathic pain in leprosy is also considered a long-term sequel of the disease because it frequently occurs after antimicrobial elimination of Bacillus and affects patients who were otherwise cured and discharged from care. In the last 10 years, it has been shown that different screening tools used in neuropathic pain of other etiologies could also be used to detect pain of neuropathic characteristics in these patients. However, there is still scarce information on the clinical phenotype of neuropathic pain and whether it would differ from the neuropathic pain of other etiologies. Additionally, there is currently no evidence-based treatment for leprosy-associated neuropathic pain, which hampers formal public health policies targeted to pain control in endemic areas.

The objectives of this study are 2-fold. First, we assessed whether neuropathic pain in leprosy had a similar symptom profile as neuropathic pain of other etiologies. It has been repetitively demonstrated that neuropathic pain is a transetiological entity; therefore, one would expect leprosy patients with neuropathic pain to present similar symptom profiles compared with neuropathic pain of other causes. However, this assumption has never been formally assessed or demonstrated, and remained to be confirmed in a controlled basis. A second aim was to assess the efficacy of neuropathic pain medications regularly prescribed to leprosy patients in an off-label basis in an outpatient setting and to evaluate which pharmacological agents would potentially provide a stronger analgesic relief and constitute good candidate drug for a double-blinded randomized clinical trial.

Thus, this study aimed to characterize symptom profiles of neuropathic pain in leprosy and aimed to compare them with those of neuropathic pain due to other etiologies in age- and sex-matched individuals from the same population and to analyze the pattern of analgesic use and their efficacy in this sample of patients to detect “candidate” drugs for future clinical trials.

2. Methods

2.1. Patients

The institutional ethics committee from Instituto Lauro de Souza Lima and Hospital das Clínicas approved this study and informed consent was obtained from all participants. Patients were prospectively screened for participation at the Pain Center of Instituto Lauro De Souza Lima (leprosy center in Bauru, São Paulo, Brazil), which is a regional reference facility for a population of 356,680 inhabitants. Patients were regularly seen in an outpatient setting in the institution and were screened for participation during a regular prescheduled medical consultation. Leprosy was diagnosed when a patient had one of the following findings: skin lesions typical for leprosy; and/or thickened peripheral nerves; and/or acid-fast bacilli on slit skin smears. Patients with leprosy were then classified using the 1998 World Health Organization classification in which patients are classified as paucibacillary if they have up to 5 skin lesions and as multibacillary if they have 5 or more skin lesions based on World Health Organization diagnostic recommendations. Adult patients with neuropathic pain based on a specialist physical examination and assessment based on proposed criteria were screened for publication. Neuropathic pain was defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system. Patients were diagnosed with neuropathic pain if the pain distribution was neuroanatomically plausible and if clinical examination confirmed that negative or positive sensory signs (ie, hype/anesthesia, hypo/analgiesia, hyperalgiesia, or allodynia) were confined to innervation territory of the affected nervous structure ie, pain of neuropathic characteristics (positive Douleur Neuropathique 4 questionnaire), had leprosy (disease causing neuropathy) and sensory deficits based on a bed-side physical examination, which included visual inspection of muscle atrophy and wasting, and cold (metal tuning fork) mechanical detection (Von Frey monofila-

2.2. Clinical assessments

Leprosy and nonleprosy neuropathic pain patients were evaluated at a baseline visit (visit 1) for the presence of neuropathic pain based on a clinical assessment. Leprosy patients were invited to return for a second visit from 3 to 5 months after visit 1 if they had moderate/severe neuropathic pain (neuropathic pain symptom inventory [NPSI] > 30).
2.2.1. Study design

2.2.1.1. Visit 1

A leprosy specialist performed clinical diagnosis of leprosy and classified the participant according to Ridley–Jopling system. All patients with clinical diagnosis of neuropathic pain were asked to fill out the NPSI questionnaire assisted by a blinded dermatologist. Leprosy patients presenting moderate to severe neuropathic pain (NPSI > 30) had analgesic treatment implemented. The choice of drug treatment, dosing, and titration method was at each treating physician’s discretion, which had no role in the study. Those with low pain intensity had their treatment maintained as it was, or received minor adjustments and were no longer assessed in the study. Nonleprosy neuropathic pain patients were evaluated by a pain specialist and also filled out the NPSI.

2.2.1.2. Visit 2

Leprosy patients who had significant pain on visit 1 and had analgesic treatment changes or implementation were reassessed and filled in the NPSI and the brief pain inventory. The BPI included questions on the intensity of the current pain, pain in the last week at its worst, at its least, and on average using a numeric rating scale (0–10). Also, pain interference in general activity, walking, mood, sleep, work, relationship with others, and enjoyment of life was rated using the same 11-point Likert scale.

2.3. Evaluation of neuropathic pain symptom profile between groups on visit 1

2.3.1. Neuropathic pain symptom inventory analysis of leprosy and nonleprosy patients and neuropathic pain symptom comparisons

Each item of the NPSI questionnaire was compared between leprosy and nonleprosy patients. Cronbach alpha from the NPSI questionnaire responses was used to assess internal consistency and reliability. Then, clusters of NPSI questionnaire symptoms from leprosy patients with neuropathic pain were compared with clusters of NPSI symptoms from patients with defined neuropathic pain of other etiologies.

2.3.2. Burden of neuropathic pain

Leprosy patients who had significant pain and were not clinically experiencing leprosy reactions were invited for a second visit and had their NPSI scores assessed for correlation with pain-related
2.4. Evaluation of treatment response

2.4.1. Effect of pharmacological treatment in neuropathic pain in leprosy

Patients with leprosy and pain were offered pharmacological treatment at the discretion of their treating physician. The name of the drugs, its dosage, and the total number of medications were recorded using the BPI. The effect of treatment in neuropathic pain was measured by the percentage of improvement in pain obtained by pharmacological treatment as measured by the BPI (0%–100% improvement, item 8) during visit 2.

2.4.2. Analgesic effect of pharmacological treatment of neuropathic pain in leprosy patients

At visit 2, the percentage of pain improvement from BPI (question 8) was used to build a score (percentage of improvement) from BPI given by the patient. These scores were recorded as the therapeutic successes for neuropathic pain treatment of all possible combinations of drugs. The drug combinations were assessed by their frequency; combinations used by at least 4 patients were presented in a descriptive output highlighting drugs with the highest analgesic effect.

2.5. Statistical analysis

Data were expressed as mean ± SD for continuous quantitative variables and as percentage for categorical variables. Normality was assessed using the Kolmogorov–Smirnov test ($P < 0.05$). Non-parametric data were compared using Mann-Whitney $U$ test for paired data and the Kruskal–Wallis test for group comparisons (leprosy vs nonleprosy-related neuropathic pain). Analyses were performed using SPSS 20.$^{20}$ Cluster analysis was carried out in order to further confirm the findings from nonparametric group comparisons (Supplementary material-1, Available at: http://links.lww.com/PR9/A14) with objective to assign observations from a sample or to a population to groups in such a way that observations within each group (called a cluster) were more similar or homogeneous to each other than to those in other groups (clusters) regarding the variables (features) that were measured.$^{17}$ Hierarchical cluster analysis was performed to identify similarities in the individual response to NPSI on symptoms profiles. The algorithm generated the preclusters which are clusters from the original cases, replacing them with the objective of reducing the number of cases for the next step and decreasing the size of the array that contains the distances between all possible cases matched. This strategy represented an approach to sequential grouping. The algorithm scanned the records one by one and decided whether a certain record should merge with the previously formed clusters or give rise to a new cluster based on the distance criteria. After the preclustering was completed, all cases in the same precluster were treated as a single entity with a technique based on their characteristics and then they are used as new cases. The size of the distance’s matrix was then no longer dependent on the number of cases, but on the number of preclusters. The 2-step method scored the quality of clustering with values between 0 and 1: dimensionless value. The closer to 1, the better was the clustering, with fewer cases being left out of the identified clusters.

### Table 1

| Symptoms                  | NeP leprosy | NeP nonleprosy | $P$  |
|---------------------------|-------------|----------------|------|
| Burning                   | 4.2 ± 4.0   | 4.7 ± 3.2      | 0.514|
| Squeezing                 | 2.4 (3.7)   | 3.4 ± 3.7      | 0.056|
| Pressure                  | 3.1 ± 3.9   | 4.0 ± 4.0      | 0.147|
| Electric shock            | 4.1 ± 4.1   | 4.2 ± 3.9      | 0.935|
| Stabbing                  | 2.9 ± 3.9   | 3.5 ± 4.0      | 0.373|
| Provoked by brushing      | 2.6 ± 3.8   | 4.1 ± 3.8      | 0.009*†|
| Provoked by pressure      | 5.9 ± 4.0   | 4.2 ± 4.1      | 0.006*†|
| Provoked by cold          | 1.5 ± 3.1   | 2.7 ± 3.9      | 0.022*†|
| Pins and needles          | 4.5 ± 3.8   | 4.5 ± 3.8      | 0.928|
| Tingling                  | 5.8 ± 4.1   | 5.3 ± 3.9      | 0.283|
| Total score               | 37.1 ± 21.2 | 40.7 ± 20.7    | 0.215|

Kruskal–Wallis test.

* $P$ was considered significant when $P < 0.05$.
† $P$ was considered not significant after Bonferroni correction $P < 0.0005$.
NeP, neuropathic pain.
4.1 ± 3.8, P = 0.009), by pressure (5.9 ± 4.0 vs 4.2 ± 4.1, P = 0.006), and by cold (1.5 ± 3.1 vs 2.7 ± 3.9, P = 0.022). These differences did not remain significant after correction for multiple analyses (Table 1 and Fig. 2).

3.3. Cluster analysis

Cronbach alpha was 0.716, showing a good reliability by responders. Hierarchical cluster analyses of NPSI scores were performed (Supplementary material-1, Available at: http://links.lww.com/PR9/A14).

3.4. Visit 2: effects of treatments on pain relief in leprosy patients

At visit 1, 52 leprosy patients had moderate to severe pain, and among those, 35 were not experiencing a clinically detectable leprosy reaction, and were then invited to attend visit 2, when the medication use profile was then assessed by the BPI, as well as the percentage of pain relief brought about by the treatment regimen. The frequency of use of each drug and the association treatments were described in Table 2.

The linear regression with LASSO analyses showed 3 coefficients with positive relationship with the percentage of pain improvement from the BPI: the first drug in Table 3 is the most relevant. Higher coefficients are associated with the importance of each drug combination to explain the percentage of pain improvement.

Considering these 3 drugs (amitriptyline, gabapentin, and chlorpromazine/haloperidol), amitriptyline and amitriptyline combined to chlorpromazine/haloperidol were the medicines with higher percentages of pain relief (66.7%). The combination of amitriptyline and gabapentin seemed to offer lower analgesic effects to patients, with greater proportions of patients without improvement (70.0% to amitriptyline + gabapentin), as expressed in Table 4.

The linear regression analysis showed that the use of amitriptyline, when effective, had the highest percentage of analgesic relief.

4. Discussion

Neuropathic pain is prevalent, affecting up to 7% of the general population. Also, it is well known that patients with chronic pain with neuropathic components have a higher negative impact in quality of life when compared with those with chronic pain conditions of similar intensity, but which lack neuropathic components. Although leprosy is rare in developed countries, it is a common cause of disability and chronic pain in developing countries such as Brazil and India. Also, leprosy is associated with neuropathic pain in a significant proportion of cases, which frequently occurs after the end of microbiological treatment of disease. In fact, it has been reported that about one-third of patients treated for leprosy more than 10 years previously had pain of neuropathic characteristics, which was severe in intensity in 40% of the cases. For this reason, neuropathic pain in leprosy is also considered as a long-term sequel of this disease, and has been proposed to be included in the care after cure program. In the past years, several studies have validated and assessed the sensitivity and specificity of screening tools habitually used to detect neuropathic pain of other etiologies in leprosy patients. These tools have been shown to be useful when used in this setting, and are currently used by some groups to screen for neuropathic pain in leprosy patients. However, the next step in the care chain in the management of these patients is lacking. Neuropathic pain is known to be responsive to antidepressants and anticonvulsants with antihyperalgesic and antiallodynic properties.

These drugs have varied efficacy, costs, side-effect profile, and

![Figure 2. Symptom profiles' comparison between leprosy neuropathic pain and nonleprosy neuropathic pain. NPSI, neuropathic pain symptom inventory.](image-url)

**Table 2**

| Drug                     | Frequency |
|--------------------------|-----------|
| Gabapentin               | 8         |
| Amitriptyline            | 6         |
| Amitriptyline and chlorpromazine/haloperidol | 6 |
| Amitriptyline + gabapentin | 10      |
| Amitriptyline, gabapentin, and chlorpromazine/haloperidol | 7 |

**Table 3**

| Drug combination                                      | Coefficient  |
|-------------------------------------------------------|--------------|
| Amitriptyline                                         | 0.02722710659 |
| Amitriptyline and chlorpromazine/haloperidol          | 0.000000000442 |
| Gabapentin                                            | 0.000000000002 |
| Amitriptyline, gabapentin, and chlorpromazine/haloperidol | 0.00000102655 |
| Amitriptyline + gabapentin                            | 0.00000419196 |

LASSO, least absolute shrinkage and selection operator.
Another issue that merits discussion is the definition of pharmacological agents or combinations not assessed here. Neuropathic pain symptoms, which may have responded to other assessed patients with moderate to severe pain at visit 2, which detectable leprosy reaction at visit 2 (which can co-occur with information on the pharmacological treatment patients were assessed pain treatment profile and efficacy at visit 2. We have no analyses and are widely available worldwide. We have also shown to have the highest efficacy profile and recent meta-bias. On the other hand, tricyclic antidepressants have been on recall of efficacy of a group of drugs, with its inherent potential and the titration methods were not controlled for. Also, it is based on a convenience sample, and the availability of drugs, the dosages, would be a potential candidate.

Different drug regimens, we have found that amitriptyline after a cluster assessment of the pain relief provided by the leprosy patients in an uncontrolled, unblinded fashion and, we have assessed the effects of different drugs prescribed to life scenario.” We have followed this last choice. In this study, the clinical practice and explore potential drugs from this “real-life scenario.” We can observe what is currently offered to these patients in neuropathic pain caused by other etiologies. Neurotic pain caused by other etiologies.

The second step in this line of reasoning would be to assess potential drugs to be included in a drug trial. The choice of the best drug to be included in such a trial is not a trivial matter. One can perform bench studies to try to screen for potential candidate drugs, one can propose drugs based on putative mechanisms of action derived from experimental works, or one can observe what is currently offered to these patients in the clinical practice and explore potential drugs from this “real-life scenario.” We have followed this last choice. In this study, we have assessed the effects of different drugs prescribed to leprosy patients in an uncontrolled, unblinded fashion and, after a cluster assessment of the pain relief provided by the different drug regimens, we have found that amitriptyline would be a potential candidate.

Our study has obvious limitations because the sample size was a convenience sample, and the availability of drugs, the dosages, and the titration methods were not controlled for. Also, it is based on recall of efficacy of a group of drugs, with its inherent potential bias. On the other hand, tricyclic antidepressants have been shown to have the highest efficacy profile and recent meta-analyses and are widely available worldwide. We have also assessed pain treatment profile and efficacy at visit 2. We have no information on the pharmacological treatment patients were already on during visit 1. Also, despite that exclusion of clinically detectable leprosy reaction at visit 2 (which can co-occur with neuropathic pain and confound the assessment of pain), we only assessed patients with moderate to severe pain at visit 2, which has probably excluded patients with lighter and less severe neuropathic pain symptoms, which may have responded to other pharmacological agents or combinations not assessed here. Another issue that merits discussion is the definition of neuropathic pain in economically restricted areas. This is a challenge not limited to leprosy, and it opens important discussions when trying to adapt the current diagnostic grading system of neuropathic pain in regions where confirmatory tests aimed at confirmation of lesion or disease of the somatosensory system are difficult or impossible to perform. The present data collection has been undertaken before the latest diagnostic grading system recommendations. However, even if one applied these criteria to our sample of patients, we would be able to consider them as having definite neuropathic pain. The grading system requires a confirmatory test to provide the definite diagnosis of neuropathic pain, but when mentioning the effects of direct surgical lesions to nerves recognizes that “(...) direct anatomical or surgical evidence (ie, of disease or lesion to the somatosensory system) counts as a confirmatory test.” Because our patients had major limb atrophic changes due to nerve lesions in the area of neuropathic pain, one can use it as surrogate markers of abnormal confirmatory tests.

Despite these limitations, we believe that the controlled comparison of leprosy and nonleprosy neuropathic pain allows us to conclude that leprosy can cause neuropathic pain of different clinical presentations, just as any other etiology of neuropathic pain. Also, it may respond to drugs usually used to control pain of neuropathic profile and amitriptyline may constitute a candidate drug for future formal clinical trials.

Disclosures

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The institutional ethics committee at Instituto Lauro de Souza Lima approved the project number 230-A/14. All study participants provided written informed consent.

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| Medication                                      | No improvement | Improvement | Row total |
|------------------------------------------------|----------------|-------------|-----------|
| Amitriptyline                                  | 2 (0.333)      | 4 (0.667)   | 6         |
| Amitriptyline and chlorpromazine/haloperidol   | 2 (0.333)      | 4 (0.667)   | 6         |
| Gabapentin                                     | 3 (0.375)      | 5 (0.625)   | 8         |
| Gabapentin and chlorpromazine/haloperidol      | 0 (0.000)      | 1 (1.000)   | 1         |
| Amitriptyline, gabapentin, and chlorpromazine/haloperidol | 5 (0.714) | 2 (0.286)   | 7         |
| Amitriptyline e gabapentin                     | 7 (0.700)      | 3 (0.300)   | 10        |
Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A14.

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