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Agreement between the Douleur Neuropathique in 4 Questions and Leeds Assessment of Neuropathic Symptoms and Signs Questionnaires to Classify Neuropathic Pain among Patients with Leprosy

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Abstract. Neuropathic pain (NP) often occurs during the course of leprosy, and screening tools to differentiate NP from non-NP are often used. However, their performance varies in different settings. The most frequently used scales are the Douleur Neuropathique in 4 questions (DN4) and the Leeds assessment of neuropathic symptoms and signs (LANSS) questionnaires. Thus, we conducted a study to evaluate the agreement between DN4 and LANSS questionnaires to classify NP in 195 leprosy patients attending two reference centers in Sergipe, Brazil. The DN4 and LANSS classified 166 and 110 patients, respectively, as having NP. One hundred and seven (54.8%) were classified as NP by both questionnaires; 59 (30.2%) solely by the DN4 questionnaire and three (1.5%) solely by the LANSS. The agreement of the questionnaires was 66.2% (weak agreement, Kappa = 0.30). Although both questionnaires identified a high proportion of NP, the development of more robust instruments is necessary to ensure the accuracy of diagnosis of leprosy patients classified as having NP.

INTRODUCTION

Pain is one of the main reasons why people seek medical services. Acute pain leads patients to attend emergency services, whereas chronic pain is a major cause of ambulatory consultations. It is estimated that one in five adults experience pain at any one time and one in 10 patients suffer of chronic pain.[1]

Neuropathic pain (NP), or "pain arising as a direct consequence of a lesion or disease affecting the somatosensory system,"[2] is present in 1–18% of patients with pain[3] and occurs in a wide range of diseases.[4] Between 11% and 79% of patients with leprosy are reported to have NP[4–8]; and other types of pain, such as nociceptive and inflammatory pain may occur.[9] The proper classification of pain is essential for the selection of therapy, as nociceptive pain responds to steroids and anti-inflammatory drugs[10]; inflammatory pain can be treated with nonsteroidal anti-inflammatory drugs,[9] and NP responds to tricyclic antidepressants, anticonvulsants, and opioids.[11]

Although NP is a common complication of leprosy, its identification is often neglected. Screening tools to identify NP often used by nonspecialists include the Douleur Neuropathique in 4 questions (DN4) and the Leeds assessment of neuropathic symptoms and signs (LANSS) for patients with chronic pain questionnaire.[12] However, few studies have evaluated their use in leprosy.

METHODS

We evaluated the agreement of the DN4 and LANSS questionnaires in leprosy patients using a cross-sectional survey of patients > 15 years of age with a diagnosis of leprosy attending the leprosy reference centers in Sergipe State, northeast Brazil, between February and June 2015.

All consecutive patients attending the University Hospital Clinic and the Leprosy and Tuberculosis Reference Center reporting having pain at the time of consultation were invited to participate. Patients were enrolled if they were receiving multidrug therapy (MDT) or had completed treatment but were attending the services to complete routine follow-up consultations. Patients with diabetes, alcoholism, human immunodeficiency virus infection, or severe mental or physical conditions interfering with the assessment of pain were excluded. The patient's demographic and clinical characteristics (leprosy classification, disability grade, leprosy reaction) were obtained using structured questionnaires. Patients were classified according to World Health Organization (WHO) criteria as paucibacillary (PB) (≤ 5 skin lesions and/or only one affected nerve trunk) or multibacillary (MB) leprosy (> 5 skin lesions and/or > 1 affected nerve trunk).[13] Leprosy reactions were classified as type 1 (acute episodes of skin or nerves inflammation) or type 2 (appearance of painful skin nodules with or without neuritis).[13] WHO categorizes leprosy-related disability as having no disability (grade 0); decreasing or loss of sensibility in the eyes, hands, or feet without visible deformity (grade 1); and loss of sensation and visible deformities of the eyes, hands, or feet (grade 2).[14]

Participants were assessed for skin sensory loss and enlargement of peripheral nerves by assessing touch, pinprick sensations, mechanical allodynia, and nerve palpation. Two trained research assistants applied the LANSS and DN4 questionnaires in Portuguese. The LANSS questionnaire evaluates five symptoms and two sensory tests for the presence of allodynia, hyperesthesia, or hypoesthesia to pinprick.[12] This tool indicates that "if (the) score < 12, neuropathic mechanisms are unlikely to be contributing to the patient's pain" and "if (the) score ≥ 12, neuropathic mechanisms are likely to be contributing to the patient's pain."[12] The DN4 questionnaire distinguishes NP and nonneuropathic (non-NP) pain using seven items related to symptoms (burning, painful cold, electric shock, tingling, pins and needles, and itching) and three items related to the clinical examination (hypoesthesia to touch and prick and

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brushing).[12] The score ranges from 0 to 10, with scores ≥ 4 suggesting NP.[12]

Categorical variables were described using frequencies and percentages. The agreement between the two instruments was calculated by dividing the number of concordant positive and concordant negative cases by the total number of patients and estimating Kappa statistics.[15] P values < 5% were considered statistically significant.

The Human Research Ethics Committee of the Federal University of Sergipe (CAAE n.31078114.3.0000.5546) approved the study protocol. Written informed consent was obtained from all participants. Parents or guardians provided written informed consent for minors.

RESULTS

One hundred and ninety-five patients with a median (interquartile range) age of 49 (25–75) years were enrolled, of whom 120 (61.5%) were male. One hundred and fifty-nine (81.5%) had MB and 35 (17.9%) had PB leprosy. Eighty-two (42%) patients were receiving MDT and 113 (58%) had completed treatment. In total, 131 (67.2%) patients had leprosy-related disabilities and 130 (66.7%) had leprosy reactions (Table 1).

The DN4 questionnaire classified 166 (63.8%) patients as having NP, with numbness (163, 98.2%), tingling (150, 90.4%), pins and needles (137, 82.5%), and prick hypoesthesia (137, 82.5%) being most frequently reported (Table 2). The LANSS questionnaire classified 110 (42.3%) patients as having NP. The symptoms more frequently reported were pins and needles, electric shocks, and tingling (110, 100%), shootings (102, 92.7%), and burnings (95, 86.4%), as shown in Table 2.

The DN4 questionnaire classified 138 (86.8%) of 159 MB leprosy patients as having NP, whereas the LANSS classified 93 (58.5%) as having NP. Among the 131 patients who had leprosy reactions, 74 (56.5%) were classified as having NP by both DN4 and LANSS questionnaires.

The agreement of the scales to classify patients as having NP was 66% among PB leprosy patients (Kappa = 0.32, P = 0.02), 69% among MB patients (Kappa = 0.30, P < 0.001), 67% among the patients without leprosy reactions (Kappa = 0.30, P = 0.003), and 68% among the patients with leprosy reactions (Kappa = 0.30, P < 0.001). The overall agreement of the two scales is shown in Table 3. One hundred and seven (54.8%) patients were classified as NP by both questionnaires; 59 (30.2%) solely by the DN4 questionnaire; three (1.5%) solely by LANSS, and 26 (13.3%) as non-NP by both scales. The overall agreement was 66.2% (129/195), with a Kappa of 0.30 (P < 0.001) corresponding to weak agreement.

TABLE 1
Demographic and clinical characteristics of study participants

Variables	N = 195
Age, median (IQR)	49 (36–59)
Sex, male, *n* (%)	120 (61.5)
Income, *n* (%)	
0–2 minimum salaries	185 (95.4)
≥ 3 minimum salaries	9 (4.6)
Schooling	
0–4 years	150 (76.9)
5–8 years	39 (20.0)
≥ 9 years	6 (3.1)
Rural residency	41 (21.0)
MB leprosy (%)	159 (81.9)
Leprosy reactions	157 (60.4)
Presence of disability	131 (67.2)

IQR = interquartile range; MB = multibacillary.

TABLE 2
DN4 and LANSS questionnaire responses of patients classified as having NP and non-NP

DN4 items	Score ≥ 4 (NP) *N* (%)	Score < 4 (non-NP) *N* (%)
Burning	132 (79.5)	6 (20.7)
Painful cold	56 (33.7)	0 (0)
Electric shocks	133 (80.1)	11 (37.9)
Tingling	150 (90.4)	9 (31)
Pins and needles	137 (82.5)	6 (20.7)
Numbness	163 (98.2)	14 (48.3)
Itching	81 (48.8)	3 (10.3)
Touch hypoesthesia	127 (76.5)	6 (20.7)
Prick hypoesthesia	137 (82.5)	8 (27.6)
Pain increasing by brushing (allodynia)	31 (18.7)	1 (3.4)
LANSS items	**Score ≥ 12 (NP) *N* (%)**	**Score < 12 (non-NP) *N* (%)**
Pins and needles, electric shocks and tingling	110 (100)	64 (75.3)
Autonomic changes	88 (80)	7 (8.2)
Pain evoked by light touching	33 (30)	5 (5.9)
Electric shocks or shooting	102 (92.7)	51 (60)
Hot or burning	95 (86.4)	47 (55.3)
Allodynia	18 (16.4)	0 (0)
Raised pin prick threshold	92 (83.6)	55 (64.7)

DN4 = Douleur Neuropathique in 4 questions; LANSS = Leeds assessment of neuropathic symptoms and signs; NP = neuropathic pain.

DISCUSSION

The recognition of NP in leprosy patients is important for the selection of adequate treatment. The reported prevalence of NP in leprosy patients, however, varies widely.[4,8,9,16,17] These estimates are likely to vary by the type of participants and the diagnostic tools used.[9] The DN4 questionnaire is reported to have high sensitivity (100%)[4] but variable specificity (45–92%)[4–6,18]; whereas the LANSS questionnaire is reported to have slightly lower sensitivity (85%) and specificity (42%).[4]

Although screening tools offer screening guidance for the potential presence of NP, their use should not replace clinical judgment, which is considered the reference standard by experienced clinicians. There are very few studies comparing the performance of the DN4 and LANSS questionnaires in patients with leprosy.[4] Although in this study, both

TABLE 3
Frequencies of positive/negative findings for DN4 and LANSS questionnaires

	DN4 questionnaire		
LANSS questionnaire	Positive	Negative	Total
Positive	107 (53.3%)	3 (1.5%)	110
Negative	59 (30.2%)	26 (13.3%)	85
Total	166	29	195

DN4 = Douleur Neuropathique in 4 questions; LANSS = Leeds assessment of neuropathic symptoms and signs; Kappa = 0.30; P < 0.001.

questionnaires classified a high proportion of patients as having NP, they presented a high level of disagreement.

Most studies use different reference standards to assign patients as correctly and incorrectly classified and the lack of a uniform reference standard impedes their comparison. The high level of disagreement reported here indicates that studies using only one scale present risk of misclassifying or missing patients with NP because the scales seems to select different patients for referral.

A study evaluating the agreement between the self-completed LANSS, which does not include clinical examinations, and the DN4 questionnaire in patients with low back-related leg pain, reported that the DN4 was slightly more discriminatory to identify NP.[19] A further study applying the DN4 with and without clinical examination in the same patients identified that omitting the clinical component led to differences in sensitivity and specificity and reduced the diagnostic accuracy when compared with an expert-led clinical evaluation.[20]

In our study, both questionnaires included a brief clinical examination. The DN4 questionnaire classified 25% more patients as having NP than the LANSS. Perhaps, its higher propensity to classify patients as NP is due to the additional parameters assessed such as numbness, itching, and soft touch threshold.[7] In addition, the DN4 questionnaire is composed of short questions and symptoms that are well distributed throughout the questionnaire, which facilitate the patient's understanding of the questions.

Studies based on populations attending reference and specialized centers are more likely to have leprosy lesions and complications than patients treated at primary health centers and therefore are more likely to have NP.[7,8] There is also a well-established association between the presence of leprosy reactions and pain,[4,9] and it is presumed that NP develops gradually as a consequence of the regenerative processes leading to overactive peripheral nociceptive fibers resulting from chronic neural inflammation.[4]

The main limitation of this study therefore concerns with sample selection, as participants were attending reference centers and were more likely to have NP than patients attending primary care facilities. Scales that have a high proportion of false-positive results may return overoptimistic assessments in this context. Furthermore, the scales evaluated only distinguish NP from non-NP pain. However, patients with leprosy often have other non-NP pain types over the clinical course of their illness, and further scales are needed to fully classify these patients.

The instruments assessed here are widely used to help nonspecialist health-service providers to identify patients who may have NP. They are easy to use in locations where there are no specialists available to screen patients for referral to specialized centers. Despite their lack of agreement, health staff does not have better scales available and will need to continue using them until improved tools become available. However, staff needs to be aware of their significant limitations.

In conclusion, DN4 and LANSS questionnaires have a substantial degree of disagreement to classify NP in leprosy patients. More robust and accurate screening tools suitable for use by nonspecialist health providers to identify NP are needed.

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