Comparative study of the cutaneous sensation of leprosy-suspected lesions using Semmes–Weinstein monofilaments and quantitative thermal testing

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Summary The objective of the present study was to compare the warm cold perception thresholds (WPT), cold perception thresholds (CPT) and the warm and cold perception interval (WCPI) determined in our previous study with the touch-pressure thresholds, in leprosy-suspected skin lesions (‘patch’). Thermal testing was conducted using a thermal sensory analyser TSA-2001 (Medoc Ltd., Israel) and the method of levels. The touch-pressure thresholds were measured using Semmes-Weinstein monofilament (SWM) of 0·05 g, 0·2 g, 2 g, 4 g, 10 g and 300 g. A cross-sectional study of 112 patients presenting with leprosy-suspected skin lesions, with no clinical evidence of peripheral nerve damage, was conducted. Leprosy diagnoses were based on clinical dermato-neurological examinations. One-hundred-and-eight subjects (45 males, 63 females; average age 37·7 years) completed the tests: 82 were positively diagnosed with leprosy and 26 with diseases of different aetiologies. The SWM test showed a sensitivity of 81·7% and a specificity of 96·1%, while the warm and cold perception thresholds presented sensitivity of 90·2% and 92·2%, respectively (both with 100% specificity). In leprosy patients, lesions that exhibited pressure thresholds of 0·05 g typically showed significantly different WPT, CPT and WCPI values when compared with skin lesions of different aetiologies. The SWM test showed a sensitivity of 81·7% and a specificity of 96·1%, while the warm and cold perception thresholds presented sensitivity of 90·2% and 92·2%, respectively (both with 100% specificity). In leprosy patients, lesions that exhibited pressure thresholds of 0·05 g typically showed significantly different WPT, CPT and WCPI values when compared with skin lesions of different aetiologies. Within the leprosy group, the mean values of WPT, CPT and WCPI increased according to the increase in touch-pressure thresholds. Some of the patients exhibiting leprosy lesions with touch-pressure thresholds of 0·05 and 0·2 g presented normal WPT or CPT values. However, all patients with SWM equal or above 2·0 g presented altered WPT and CPT. All patients with leprosy, including those that exhibited pressure thresholds of 0·05 g, presented altered WCPI in the skin lesions. Despite a higher sensitivity to thermal tests, the SWM has adequate validity as a screening tool in the diagnosis of leprosy.

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Introduction

Hansen’s disease or leprosy is an infectious disease with insidious evolution caused by *Mycobacterium leprae*, which affects the peripheral nervous system, skin, and other tissues.1–4

The cardinal signs of the disease are cutaneous lesions with altered sensation, enlargement of the peripheral nerve, and slit skin smears showing alcohol-acid fast bacilli.1–4 The diagnosis of leprosy can also be established by the demonstration of a marked reduction in tactile, thermal or pain sensitivity.1–5 In the early stages, temperature and pain sensation of the lesions may be reduced while touch is maintained.5,6

Sensation in leprosy (skin lesions and areas supplied by major nerve trunks) lesions can be measured using SWM to measure touch-pressure thresholds, as well as standard clinical sensory tests employing cotton wool to evaluate tactile sensation (large myelinated A-beta fibres), pins to evaluate pain sensitivity (small myelinated A-delta and unmyelinated C fibres), and tubes containing hot (45°C) and cold (4°C) water to evaluate thermal sensation (small myelinated A-delta and unmyelinated C fibres). The technique involving warm/cold water is frequently disregarded in some services.

The SWM kit consists of monofilaments standardised to deliver forces of 0·05 g (green), 0·2 g (blue), 2 g (purple), 4 g (red), 10 g (orange) and 300 g (magenta). Normal reference value is 0·05 g in any region of the body except for the soles of the feet (2·0 g).

In a previous study,9 we reported the warm perception threshold (WPT) and the cold perception threshold (CPT), and determined the warm and cold perception interval (WCPI) of leprosy-suspected lesions, using a TSA-2001 thermal sensory analyser (Medoc Ltd, Israel) and the method of levels.10 The cut-off points for WPT, CPT and WCPI determined from the ROC curve (receiver operating characteristic) were 35·10°C, 28·95°C and 6·10°C, respectively. WPT ≤ 35·10°C, CPT ≥ 28·95°C and WCPI ≤ 6·10°C were considered as normal. Furthermore, the absolute differences were established between the WCPI of a suspected lesion and the WCPI of contralateral skin areas without lesion (SAWL), the WCPI of a suspected lesion and homolateral SAWL, and the WCPI of contralateral and homolateral SAWL. In the group of leprosy-diagnosed patients, the minimum absolute difference between the WCPI of lesions and the WCPI of contralateral or homolateral SAWL, the WCPI of lesions of different aetiologies and of contralateral SAWL, and the WCPI of contralateral and homolateral SAWL was found to be 4·6°C (ROC curve; cut-off point of 2·95°C). Such a temperature difference was 2·5-times larger than the greatest difference (1·8°C) recorded in the control group between the WCPI of lesions of different aetiologies and the WCPI of homolateral SAWL, the WCPI of lesions of different aetiologies and of contralateral SAWL, and between the WCPI of contralateral and homolateral SAWL of all patients. WPT > 35·10°C and CPT < 28·95°C reflected the involvement of the unmyelinated C fibres and small myelinated A-delta fibres, respectively, while the WCPI > 6·10°C and absolute differences of WCPI > 2·95°C reflected the involvement of the C fibres or A-delta fibres or both. Although normal WPT or CPT values were recorded in leprosy-diagnosed patients, none of the individuals presented normal WCPI values.

The objective of the present study was to compare the WPT, CPT and WCPI values determined in our previous study with the touch-pressure thresholds obtained using the SWM.
technique. Since a significant number of patients could not define with certainty the precise time of evaluation of their skin lesions, it was considered, for the purpose of the present study, that early lesions were those patients with skin lesions with no signs or symptoms involving major nerve trunks.

Patients and methods

PATIENTS

A cross-sectional study involving 112 patients from various leprosy health centres located in the metropolitan area of Belo Horizonte (MG, Brazil) was performed during the period between January 2000 and November 2004. Details of the project were presented to and approved by the Ethical Committee of UFMG, and all potential subjects were required to sign an appropriate form containing the Terms of Consent prior to the commencement of the study. Patients aged more than 7 years and with leprosy-suspected skin lesions with diameters >18 mm (i.e. providing a thermal stimulation area of at least 16 × 16 mm) were included in the study. Patients with neurological impairments or with clinical histories of alcoholism, diabetes mellitus and other metabolic or genetic disorders, which could result in the impairment of the central and peripheral nervous system, were excluded.

For each patient, SWM values (at 0.05, 0.2, 2.0, 4.0, 10.0 and 300.0 g) at selected leprosy-suspected lesions and the corresponding SAWL areas were determined. The areas examined were marked with a pen, and patients were immediately redirected to the Clinical Neurophysiology Laboratory of the Orthopaedic Hospital (Belo Horizonte) so that the thermal thresholds of the lesions could be measured. For patients presenting with multiple lesions, one lesion with an area suitable for application of the thermal testing and subsequent biopsy was selected for this study. After the thermal studies had been completed, patients returned to their original health centres to receive a definitive diagnosis and specific treatment. In order to guarantee the blind nature of the study, the hospital laboratory technicians did not have access to the results of the investigations carried out at the health centres.

LEPROSY DIAGNOSIS

The diagnosis of leprosy was based on the clinical dermo-neurological examination together with complementary examinations including skin biopsy and histopathology, slit skin smears, evaluation of SWM, Mitsuda reaction, anti PGL-1 serology (ML flow), and histamine and pilocarpine tests. A further period of observation was required before a definitive diagnosis could be reached for some patients. In all cases, data collected at the health centres and at the hospital were analysed only after a definitive diagnosis had been achieved.

DETERMINATION OF TOUCH-PRESSURE THRESHOLD

The SWM test was applied to suspected lesions and to contralateral and homolateral SAWL of the subjects by three different testers, all highly experienced in leprosy. The evaluation began with a monofilament providing the lowest force, and this was perpendicularly applied to the skin area until it bent in a rhythmic and regular manner. The time interval between initial contact of the monofilament with the skin and its removal was approximately 1 s for
each application. Green (0·05 g) and blue (0·2 g) monofilaments were applied three times while the others were applied only once. The patient was asked if the contact with the monofilament had been perceived: two positive responses following three independent contacts were considered as a valid perception. In the absence of a positive response, a new monofilament of a greater force was applied. The results were recorded in terms of the monofilament corresponding to the first force that was perceived by the patient. Patients had no visual contact with the region being examined throughout the procedure.

STATISTICAL ANALYSIS

The mean values of WPT, CPT and WCPI obtained for leprosy-diagnosed patients and control groups were stratified according to SWM thresholds and compared by descriptive analysis, including 95% confidence intervals. For leprosy-diagnosed patients, the proportions exhibiting normal and altered thermal thresholds, evaluated according to the established WPT, CPT and WCPI cut-off points, were compared with the proportion of patients presenting normal and altered pressure thresholds.

Results

One hundred and twelve patients presenting with leprosy-suspected skin lesions were redirected to the Clinical Neurophysiology Laboratory, and 108 (45 males and 63 females) concluded all of the tests. The age of patients with leprosy-suspected skin lesions ranged from 9 to 73 years (37·7 ± 14·9 years). The average age of patients with leprosy was 37·4 ± 13·2 years and the group without leprosy was 38·7 ± 18·7 years. Leprosy was subsequently diagnosed in 82 (75·9%) patients, while 26 were diagnosed with vitiligo, pityriasis alba, granuloma annulare, atopic dermatitis, pseudo-lymphoma, post-inflammatory residual dischromia and fungal mycosis. Leprosy lesions predominated on the lower limbs (36·6%), followed by the upper limbs (31·7%), trunk (24·4%) and face (7·3%). The lesions were characterized as indeterminate type (13·4%), tuberculoid type (28%), borderline tuberculoid type (51·2%) and borderline borderline type (7·3%). The number of suspected skin lesions per patient varied between one and eight: 37 patients presented only one lesion, amongst whom 15 were confirmed with leprosy.

When skin lesions of the 82 leprosy-diagnosed patients were tested with SWM, 18·3% of the subjects could perceive the 0·05 g monofilament, while the 0·2 g monofilament was the first perceived by 23·2%, the 2 g monofilament by 24·4%, the 4 g monofilament by 18·3%, and the 10 g monofilament by 8·5%. Of this group, 7·3% could only perceive the 300 g monofilament. The SWM test in skin lesions presented a sensitivity of 81·7% and a specificity of 96·1%.

The contralateral and homolateral SAWL of most of the individuals (99·07%) within the leprosy-diagnosed and the non-leprosy groups presented monofilament thresholds of 0·05 g, although two patients presented thresholds of 0·2 g. Amongst the 26 patients in the non-leprosy group who presented lesions of diverse aetiologies, 25 perceived the 0·05 g monofilament, and one (a patient with fungal mycosis) perceived the 0·2 g monofilament.

When non-leprosy skin lesions and SAWL (in the leprosy-diagnosed and the non-leprosy groups) exhibiting monofilament thresholds of 0·05 g were compared, the WPT, CPT and WCPI values of such areas and lesions were not statistically different. In the two SAWL and
in the non-leprosy skin lesion (fungal mycosis), in which the threshold was the 0.2 g, the WPT, CPT and WCPI values were similar to those determined for non-leprosy skin lesions and SAWL of all patients in which the threshold was the 0.05 g. On the other hand, when leprosy skin lesions presenting monofilament thresholds of 0.05 g were compared with skin lesions of diverse aetiologies, the mean values of WPT, CPT and WCPI were found to be significantly different. For leprosy skin lesions, the mean values of WPT, CPT and WCPI increased proportionally with the increase in monofilament threshold (Table 1).

Although the mean values of WPT, CPT and WCPI for lesions of different aetiologies were statistically different from those obtained for the leprosy-lesions, overlap of the confidence intervals was observed in the leprosy group following stratification according to monofilament threshold (Table 1).

Fifteen (18.3%) of the leprosy patients presented lesions with apparently normal pressure thresholds (i.e. they could perceive the 0.05 g monofilament). Within this set of patients, five showed normal WPT values (≥35-10°C) and 10 exhibited altered WPT, three showed normal CPT values (≥28-95°C) and 12 exhibited altered CPT, but all 15 presented altered WCPI values (>6-10°C) (Table 2).

A further set of 19 patients were able to perceive the 0.2 g monofilament during the assay of leprosy skin lesions, and within this set three had normal WPT and 16 had altered WPT, three had normal CPT and 16 had altered CPT, but all 19 presented altered WCPI values. The remaining leprosy patients presented lesions with altered WPT, CPT and WCPI values (Table 2).

**Discussion**

Quantitative sensory testing, amongst which thermal and SWM techniques are included, enables evaluation of the function of the afferent nervous system that encompasses the cutaneous receptors, peripheral fibres and central nervous system (CNS) connections. Under standardised conditions these tests are considered reliable and reproducible.10–18 While these

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### Table 1. Means, with respective standard deviations and confidence intervals (in parenthesis), of the warm perception threshold (WPT), cold perception threshold and warm cold perception interval (WCPI) stratified according to the Semmes-Weinstein monofilament (SWM) thresholds presented by leprosy and non-leprosy-diagnosed patients

<table>
<thead>
<tr>
<th>SWM (g)</th>
<th>WPT (°C)</th>
<th>CPT (°C)</th>
<th>WCPI (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.05</td>
<td>33.28 ± 0.70 (33.00; 33.57)</td>
<td>30.85 ± 0.88 (30.49; 31.20)</td>
<td>2.43 ± 1.11 (1.98; 2.87)</td>
</tr>
<tr>
<td>0.05</td>
<td>39.54 ± 5.34 (36.58; 42.50)</td>
<td>18.41 ± 11.33 (12.13; 24.68)</td>
<td>21.13 ± 11.25 (14.90; 27.36)</td>
</tr>
<tr>
<td>0.2</td>
<td>42.79 ± 5.43 (40.18; 45.41)</td>
<td>16.40 ± 11.66 (10.78; 22.02)</td>
<td>26.38 ± 15.97 (18.68; 34.08)</td>
</tr>
<tr>
<td>2</td>
<td>46.95 ± 4.26 (44.95; 48.94)</td>
<td>7.80 ± 8.98 (3.60; 12.00)</td>
<td>39.25 ± 12.47 (33.41; 45.09)</td>
</tr>
<tr>
<td>4</td>
<td>49.85 ± 0.49 (49.58; 50.12)</td>
<td>2.61 ± 7.01 (−1.27; 6.50)</td>
<td>47.74 ± 7.45 (43.11; 51.37)</td>
</tr>
<tr>
<td>10</td>
<td>49.87 ± 0.34 (49.56; 50.19)</td>
<td>1.11 ± 2.95 (−1.61; 3.84)</td>
<td>48.76 ± 3.29 (45.72; 51.80)</td>
</tr>
<tr>
<td>300*</td>
<td>50.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>50.0 ± 0.0</td>
</tr>
</tbody>
</table>

*The confidence interval was not determined owing to the constant values of WPT, CPT and WCPT.*
tests are not specific to evaluate the function of the peripheral nervous system, since they all evaluate the afferent nerve system, they are useful in the study of focal and generalised peripheral neuropathies of any aetiology. In leprosy, the sensation in the skin may be reduced due to dermal and truncal nerve fibre involvement. In order to avoid truncal nerve involvement, homolateral SAWL in the control group, whenever possible, belonged to the same peripheral field of trunk nerve where suspect lesions were present (e.g. in one skin lesion on a leg medial part, the comparison spot was established as an area of saphenous nerve). While determining the thermal threshold, a thermal isolating tape was used around the thermode. Initial studies showed that patients with leprosy skin lesions with a size similar to the thermal stimulator, perceived warm and cold sensation through the skin surrounding the lesion.

The results derived from quantitative thermal testing show that WPT, CPT and WCPI values of leprosy skin lesions are typically increased compared with skin lesion of other aetiologies and SAWL. Some leprosy skin lesions presented normal WPT values while others exhibited normal CPT values, the WCPI parameter, which evaluates both types of fibres and therefore both types of stimuli (warm and cold), always showed altered values. The WCPI value is the best indicator of thermal sensation, a term employed in the literature as a non-specific expression that does not describe warm and cold stimuli explicitly in terms of units of temperature.

The values (normal or abnormal) of WPT, CPT and WCPI were determined from ROC curves. In the present study, normal tactile sensation in the skin lesions (defined by the perception of a 0.05 g monofilament) was recorded for 18.3% of leprosy skin lesions and for 96.2% of skin lesions of diverse aetiologies. The WPT, CPT and WCPI values of leprosy skin lesions in those patients who perceived the 0.05 g monofilament were significantly different from those obtained for lesions of diverse aetiologies. These data may indicate that the afferent nerve system of the tactile sensation was preserved even though thermal sensation was impaired. Amongst the leprosy patients with normal tactile sensation, 6.1% had no alteration in WPT values and 3.7% had no alteration in CPT values, indicating that the unmyelinated C fibres and small myelinated A-delta fibres (or specific receptors), respectively, maintained their basic functions. Although most of the leprosy patients who perceived the 0.2 g monofilament had increased WTP, CPT and WCPI values compared with those who perceived the 0.05 g monofilament, some had normal WPT or CPT values (3.7% each).

<table>
<thead>
<tr>
<th>SWM (g)</th>
<th>WPT (n = 82) (%)</th>
<th>CPT (n = 82) (%)</th>
<th>WCPI (n = 82) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 35°C (normal)</td>
<td>&gt; 35°C (abnormal)</td>
<td></td>
</tr>
<tr>
<td>0.05</td>
<td>5 (6.1%)</td>
<td>10 (12.2%)</td>
<td>3 (3.7%)</td>
</tr>
<tr>
<td>0.2</td>
<td>3 (3.7%)</td>
<td>16 (19.5%)</td>
<td>3 (3.7%)</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>20 (24.4%)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>15 (18.3%)</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>7 (8.5%)</td>
<td>0</td>
</tr>
<tr>
<td>300</td>
<td>0</td>
<td>6 (7.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>8 out of 82</td>
<td>74 out of 82</td>
<td>6 out of 82</td>
</tr>
</tbody>
</table>

The values (normal or abnormal) of WPT, CPT and WCPI were determined from ROC curves.
Only patients diagnosed with leprosy were unable to perceive the 0.2 g monofilament, these patients presented altered WPT and CPT values compared with non-leprosy patients. As the pressure thresholds increased, the mean values of WPT, CPT and WCPI increased linearly. While there was considerable variability in the WPT and CPT values amongst leprosy patients who could perceive the 0.05 g and 0.2 g monofilaments, such variability diminished considerably in leprosy patients who only perceived the 2 g monofilament and above.

Even though altered thermal sensation may be detected during the early stages of the disease (defined as patients with skin lesions with no signs and symptoms involving major nerve trunk), for skin lesions presenting pressure thresholds of 0.05 g and 0.2 g the individual values of WPT and CPT must be considered with caution since these parameters might remain normal. Thus, for such patients, if one parameter is registered as normal, the other must be measured as well. However, in patients whose pressure threshold was 2.0, 4.0, 10.0 and 300.0 g both WPT and CPT values were altered, and such higher thresholds reflected warm and cold hypoesthesia.

Quantitative thermal testing is not appropriate for field investigations owing to the size and high cost of thermal analysers, and its application is limited to leprosy research centres. It is important to develop smaller and cheaper devices which permit information on dynamic temperature, since, cold and warmth receptors are more sensitive to change in skin temperature than to constant temperatures. Despite a higher sensitivity to thermal tests, the SWM test has adequate validity as a tool in the diagnosis of cutaneous forms of leprosy and in the selection of patients who should be submitted to a more detailed examination.

Since the results presented in this work were obtained from a study of skin lesions they cannot be extrapolated to peripheral nerve trunk function. The evaluation of patients presenting necrobiosis lipoidia, in which thermal sensation may be altered, was not evaluated in the present study.

The mechanisms responsible for the initial symptoms of leprosy involve damage to the fibres responsible for thermal sensation, but they are not well characterised. Rambukkana and co-workers report that M. leprae has a high affinity for Schwann cells, which contain four proteins, laminin-2, α-dystroglycan, β-dystroglycan and dystrophin, that may function as a bridge between the bacillus and the inner cell. The thermal and pain receptors of the skin consist basically of free nerve endings (A-delta and C fibres) that are surrounded by Schwann cells. The larger fibres responsible for tactile sensation possess non-neural encapsulated receptors and most of the fibres of peripheral nerve are small myelinated A-delta and unmyelinated B and C fibres. These factors may explain the higher sensibility to thermal tests in relation to SWM, observed in leprosy skin lesions evaluated in the present study.

In conclusion, normal WPT and CPT values were observed in some leprosy skin lesions whose pressure thresholds were 0.05 g and 0.2 g, while altered WCPI values were found in all individuals, even those presenting normal touch-pressure thresholds. All patients with SWM equal or above 2.0 g presented altered WPT and CPT.

References
