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Histopathological and clinical findings in leprosy patients with chronic neuropathic pain: a study from Hyderabad, India

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Summary

Background  Chronic neuropathic pain in leprosy patients after completion of multi-drug therapy (MDT) is an under-researched problem. The reason why some leprosy patients develop it is unknown. In this study we evaluated the role of ongoing inflammation and small-fibre neuropathy as possible contributing factors for neuropathic pain.

Methods  We assessed chronic neuropathic pain in 17 leprosy patients who had completed MDT and were attending a referral clinic in Hyderabad, India. All patients had a clinical assessment, intraepidermal nerve (IENF) assessment and quantitative sensory testing (QST), which included the testing of tactile and pinprick sensations using Semmes-Weinstein monofilaments and weighted needles method. Nine patients had a sural nerve biopsy (SNB).

Results  Thirteen patients had a glove and stocking pattern of neuropathy. All nerve biopsies showed inflammation with intraneural inflammation and perineural
thickening, and intraneural acid fast bacilli were observed in five biopsies. IENF analysis of the skin biopsy specimens in 16/17 patients showed a statistically significant reduction in IENF density ($P < 0.001$, Mann Whitney test) compared to control skin biopsies. Complete depletion of intraepidermal nerves was observed in six patients. QST also showed marked abnormalities. In 11 patients total sensory loss for all modalities was found, and in the other six patients the sensory function was seriously impaired.

Discussion There is evidence of ongoing intraneural inflammation in leprosy patients who have completed MDT. This may explain the occurrence of chronic neuropathic pain. Using IENF density measurement we have found significant small-fibre neuropathy in leprosy patients and the use of this tool could be expanded.

Introduction

Neuropathic pain is a pain condition initiated or caused by a primary lesion or dysfunction in the nervous system. Paradoxically, although leprosy is classically associated with anesthesia affecting the hands and feet, neuropathic pain may become a problem for some patients. Leprosy-related pain can be moderate or severe and occur either continuously or intermittently. It can occur in patients who have completed multi-drug therapy (MDT). It is not known why some leprosy patients develop chronic neuropathic pain. One explanation is the pathological involvement of small nerve fibres. These nerve fibres are of small calibre and normally responsible for sensation of heat and pain. It has been suggested that in early leprosy, pain and temperature sensation are diminished first, followed later by loss of tactile and pressure senses. This pattern of sensory loss suggests early involvement of small fibres due to inflammation secondary to mycobacterial invasion of the Schwann cells. Small-neuropathy (SFN) is defined on physiological or anatomical terms as a sensory neuropathy that exclusively or predominantly affects small fibres and their functions. Painful paresthesias are the commonest symptoms of both acquired and idiopathic small-fibre neuropathy. However, experienced observers have disagreed on the precise sequence of sensory loss by modalities. According to Cochrane, the order of loss is first thermal, then tactile, followed by pain and ultimately pressure sense.

Intraepidermal nerve fibre (IENF) density determination by using punch skin biopsies is a useful diagnostic test for patients with suspected SFN. The most frequently reported abnormality in neuropathies affecting epidermal innervation is a reduction in nerve fibre numbers. In addition to SFN, the alteration of IENF may also be useful in assessing the course and spatial distribution of nerve injury in other peripheral neuropathies. Significant reduction in intraepidermal fibres has been demonstrated for example in patients with HIV-related sensory neuropathy. Different methods are available for the epidermal nerve fibre analysis. The most sophisticated protocols include the use of confocal microscopy and imaging software, but the counting of epidermal fibres can also be performed using conventional microscopy. Common for all these methods is the use of immunohistochemistry with a protein gene product 9.5 (PGP 9.5) antibody. PGP 9.5 is a neuron-specific ubiquitin hydrolase, which is present in all axons, including the unmyelinated nerve endings and the epidermal nerve fibres. Hence, it serves as a tool for investigation of cutaneous innervation and axonal degeneration in peripheral neuropathies. According to the studies, quantitation of epidermal nerves has a diagnostic efficiency of 88% for patients with sensory neuropathies.
The objectives of this study were: 1) to document the parameters of neuropathic pain in leprosy patients who have completed their antimicrobial therapy, 2) to determine if leprosy patients with chronic neuropathic pain have peripheral neuropathy involving unmyelinated and small myelinated nerve fibres, 3) to explore the relationship between loss of cutaneous innervation and pain in these patients, and 4) to compare the findings of intraepidermal nerve analysis and sural nerve biopsy in different types of leprosy patients.

Materials and methods

Case definitions and exclusions

Patients who had completed antimicrobial treatment and were complaining of pain and dysesthesia were recruited at the Blue Peter Research Centre in Hyderabad, India. Of these patients, only those with neuropathic pain lasting at least 6 months and scoring current pain intensity $\geq 4/10$ by 11-point Likert scale were included in the study. The patient intake covered the spring of 2003. The diagnosis of leprosy was made clinically and supported histologically with patients classified according to the Ridley-Jopling scale. Exclusion criteria included treatment with thalidomide or other neurotoxic drugs, known HIV infection, hereditary neuropathy, central nervous system disease, diabetes (screening with urine glucose test), hypothyroidism (screening with blood TSH levels), known thiamine or B$_{12}$ deficiency, or a history of alcohol abuse. Patients with concomitant nociceptive pain condition (i.e. joint disease, painful ulcers, osteomyelitis) that might have complicated the pain analysis were also excluded.

Clinical assessment and quantitative sensory testing

The location of pain was recorded by using pain drawings (Figure 1).

Patients were asked about the type(s) of their pain (constant or intermittent lancinating pain), and the presence of paresthesia and dysesthesia. The intensity of the various pain components and dysesthesia was assessed with verbal rating scale (mild, moderate, severe) and with 11-point Likert scale (0–10). The interference of sleep due to the pain was evaluated with 11-point Likert scale. Thickness of individual nerves was evaluated and recorded as normal or thickened. Tenderness of the nerves was recorded if it was present also when the patient’s attention was distracted or if the patient withdrew the limb while the nerve was palpated.

Sensory testing was performed assessing heat, cold, tactile, and pinprick sensation. The presence and type of mechanical allodynia (dynamic and static) was assessed. Sensations were graded as normal (unaltered), anesthetic, hypoesthetic or hyperesthetic. Heat sensation was examined with the Thermal Sensation Tester; B.S. Tech, Switzerland (TST) using a study temperature of $+50^\circ$C. Cold sensation was tested using a glass bottle filled with water, which had been kept in the refrigerator ($+4^\circ$C). Tactile and pinprick sensations were evaluated both qualitatively and quantitatively, the former using Semmes–Weinstein monofilaments and the latter using weighted needles method. The testing sites for quantitative tactile and pinprick testing were in the leg, ankle, knee and hip, and in the arm, wrist, elbow and shoulder and the sites of pain sensation. The weighted needle apparatus consisted of 12 weighted 23 gauge disposable needles (0.2–5.2 g). The dynamic type of mechanical allodynia was assessed using a paint brush used in water colour painting and the
The patients are asked to mark these drawings according to where they hurt and to indicate which sensations they feel by referring to the key:

xxxxxx  Burning
oooooo  Pins and needles
======   Numbness
/#/#/#/   Stabbing

Figure 1. An example of pain drawing.

static type of mechanical allodynia was assessed by light compression. The terms of sensory dysfunction are explained in Table 1.

PUNCH BIOPSIES AND THEIR HISTOLOGY AND IMMUNOHISTOCHEMISTRY

A punch skin biopsy was taken from all subjects on the distal leg 10 cm above the lateral malleolus. After local infiltration of 1% xylocaine, 3 mm punch biopsy was taken with appropriate asepsis and a dressing applied. Control skin biopsies were taken from the surgical margins of seven healthy people (2 males and 5 females; age range 4–68, mean 42) having a benign nevus at Tampere University Hospital, Finland. None of the controls had a known neurological disease, diabetes, a history of alcohol abuse or use of any neurotoxic drugs (data from hospital patient records).

Specimens were fixed in 10% formalin for 4 days and then embedded in paraffin. Ten-μm sections were cut on ChemMate™ capillary gap microscope slides (Dako Cytomation
Denmark a/s, Glostrup, Denmark). Rehydrated sections were heated in a microwave oven at 850 W for two 7-minute cycles using 0·01 mol/l citrate buffer (pH 6·0) as antigen retrieval solution. For demonstration of terminal axons, a polyclonal panaxonal marker PGP 9·5 (ubiquitin hydrolase, Ultraclone, Isle of Wight, UK) was used at dilution 1:20. The immunohistochemical staining was performed using indirect streptavidin-biotin-peroxidase method in ChemMate™ 500 Immunostainer (Dako Cytomation Denmark). In negative controls primary antibody was omitted or replaced by irrelevant antisera.

The number of separate IENF was counted with a light microscope at 400x magnification by an independent observer (MK) blinded to the clinical status of the patients. The counting method has been described in previous studies.13

**NERVE BIOPSY**

Partial thickness sural nerve biopsy was taken from the ankle using standard techniques. Specimens were examined by an experienced pathologist (SS) looking for evidence of a) chronic neuritis, b) vasculitis, c) fibrosis, d) acid fast bacilli and/or debris, e) loss of small myelinated and/or unmyelinated axons. Teased fibre analysis was used in identifying pathologic conditions denoting demyelination and axonal degeneration.

**STATISTICAL ANALYSIS**

Statistical analysis was performed using SPSS for Windows version 11.0 software (SPSS Inc., Chicago, IL, USA). For each subject, IENF density was plotted against clinical symptoms. The effect of age, gender and type of leprosy on the IENF density was examined in all subjects. The concordance between the IENF and nerve biopsy was examined in 11 subjects. Difference in the number of intraepidermal nerve fibres between the groups was assessed using Mann–Whitney U and Kruskall Wallis test.

**ETHICAL CONSIDERATIONS**

The study protocol was approved by the local ethical committee of The Blue Peter Research Centre, Hyderabad. Patients were informed in detail about the possible consequences of the sural nerve biopsy (risk of infection, mild sensory abnormalities) and then invited to give written informed consent. The study was in accordance with the Helsinki Declaration of 1975.

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**Table 1. The terms of sensory dysfunction**

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paraesthesia</td>
<td>An abnormal sensation, whether spontaneous or evoked</td>
</tr>
<tr>
<td>Dysesthesia</td>
<td>An unpleasant abnormal sensation, whether spontaneous or evoked</td>
</tr>
<tr>
<td>Allodynia</td>
<td>Pain due to a stimulus, which does not normally provoke pain; divided into mechanical and thermal subtypes</td>
</tr>
<tr>
<td>Hyperalgesia</td>
<td>An increased response to a stimulus which is normally painful</td>
</tr>
<tr>
<td>Hypoalgesia</td>
<td>Diminished pain in response to a normally painful stimuli</td>
</tr>
<tr>
<td>Hyperesthesia</td>
<td>Increased sensitivity to stimulation, excluding the special senses</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>Decreased sensitivity to stimulation, excluding the special senses</td>
</tr>
</tbody>
</table>

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Results

Patients

The demographic data of the patients and subtypes of leprosy are presented in Table 2. The age range of patients was 27–69, mean 46 years. The mean time since released from therapy was four years (range 0.5–11.5 years). Nine patients had a previous history of corticosteroid use due to reactions or neuritis (mean cumulative dose 4624 mg, range 750–11250 mg). Seven patients had experienced Type I reactions (n 1–4; mean 2). Two patients had experienced type II reactions.

Characteristics of Neuropathic Pain

The distribution, duration and severity of pain are presented in Table 2. Pain was located in the extremities for all patients, but four patients also had burning facial pain. Pain was continuous in 15 patients, whereas one patient had episodic pain and another patient had disturbing dysesthesia. Pain was burning in all patients, and none had lancinating pain. In two patients the movement of a limb or an exercise caused exacerbation of pain.

The intensity of pain varied from 4 to 10 on Likert scale (mean 6.4), and pain was graded as severe by nine, moderate by four and mild by four patients. In addition to pain, one patient had touch-evoked paresthesia and 16 patients reported spontaneous paresthesia which was graded as severe by seven, moderate by five and mild by five patients. Nocturnal awakenings due to pain were reported by 15 patients, and sleep interference varied between 3 and 10 on Likert scale (mean 7.1). Continuous pain medication was used by 16 patients; 15 patients used acetylsalicylic acid and one used paracetamol.

Clinical Examination and Quantitative Sensory Testing

Findings in nerve palpation and quantitative tactile testing are presented in Table 2. All patients had more than one tender nerve on palpation (range 2–15). Pain in a glove and stocking distribution was the commonest, seen in 71% (n = 12) of patients. These patients also had corresponding sensory loss for all tested modalities in 11 cases and well preserved sensory function in one case (patient number 5). Patients with pain located in a territory of one or several nerves had sensory loss in corresponding area, but in 12 cases, a more widespread sensory loss was noticed. None of the patients had hyperalgesia or allodynia. Tendon reflexes were found to be normal in all patients. In the sensory assessment with weighted needles for pinprick sensation, eight patients did not detect any of the 12 needles in any testing site while four had well preserved sensory function (detection level below 0.65 g). The remaining five patients had diminished pinprick sensation predominantly in lower extremities.

Biopsies

Sections of the skin biopsies immunostained with a polyclonal antibody to PGP 9.5 revealed the separate IENFs and their location within the tissue. In positive control specimens, a large number of fine IENFs with good preservation of axonal morphology were found. For the analysis, the patients were divided into two groups according to their clinical findings. The first group (n = 12) comprised of patients with stocking and glove polyneuropathy, the
<table>
<thead>
<tr>
<th>Pat.nr</th>
<th>Age/gender</th>
<th>Type of leprosy</th>
<th>Time since RFT (y)</th>
<th>Distribution of pain</th>
<th>Duration of pain (y)</th>
<th>Severity of pain</th>
<th>Bacilli site</th>
<th>Number of tender nerves</th>
<th>TT (left)</th>
<th>TT (right)</th>
<th>Nerves per epidermal area</th>
<th>Inflammation in nerve biopsy</th>
<th>Reactions</th>
<th>CC (mg)</th>
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<tr>
<td>1</td>
<td>53/F</td>
<td>BT</td>
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<td>Glove and stocking</td>
<td>0.5</td>
<td>Mild</td>
<td>--</td>
<td>3</td>
<td>SL</td>
<td>SL</td>
<td>0</td>
<td>n.p.</td>
<td>0</td>
<td>0</td>
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<td>Severe</td>
<td>No bacilli seen</td>
<td>7</td>
<td>SL</td>
<td>SL</td>
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<td>Moderate</td>
<td>1 × type I</td>
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<td>Intraneural</td>
<td>9</td>
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<td>Severe</td>
<td>--</td>
<td>6</td>
<td>SL</td>
<td>SL</td>
<td>0</td>
<td>n.p.</td>
<td>0</td>
<td>0</td>
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<tr>
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<td>Intraneural</td>
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<td>2.44</td>
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<td>2 × type I</td>
<td>4465</td>
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<tr>
<td>6</td>
<td>41/F</td>
<td>BT</td>
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<td>Great toes</td>
<td>0.5</td>
<td>Mild</td>
<td>--</td>
<td>3</td>
<td>4.17</td>
<td>4.56</td>
<td>25.81</td>
<td>n.p.</td>
<td>1 × type I</td>
<td>1125</td>
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<td>44/M</td>
<td>BT</td>
<td>1.5</td>
<td>Soles, great toes</td>
<td>5</td>
<td>Severe</td>
<td>No bacilli seen</td>
<td>6</td>
<td>SL</td>
<td>SL</td>
<td>24.06</td>
<td>Intraneural</td>
<td>1 × type I</td>
<td>0</td>
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<tr>
<td>8</td>
<td>56/M</td>
<td>BT</td>
<td>1.5</td>
<td>Medial side of feet</td>
<td>4</td>
<td>Severe</td>
<td>No bacilli seen</td>
<td>9</td>
<td>4.08</td>
<td>3.61</td>
<td>37.5</td>
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<td>3 × type I</td>
<td>4650</td>
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<tr>
<td>9</td>
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<td>BT</td>
<td>3</td>
<td>Soles, V fingers</td>
<td>2</td>
<td>Mild</td>
<td>--</td>
<td>7</td>
<td>2.83</td>
<td>3.61</td>
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<td>--</td>
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<td>--</td>
<td>3</td>
<td>SL</td>
<td>SL</td>
<td>4.95</td>
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<td>1 × type I</td>
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<td>--</td>
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<td>SL</td>
<td>SL</td>
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<td>n.p.</td>
<td>4 × type I</td>
<td>9900</td>
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<td>--</td>
<td>7</td>
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<td>SL</td>
<td>9.64</td>
<td>n.p.</td>
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<td>0</td>
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<td>Intraneural</td>
<td>5</td>
<td>SL</td>
<td>SL</td>
<td>0</td>
<td>Moderate</td>
<td>0</td>
<td>0</td>
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<td>38/F</td>
<td>LL</td>
<td>1</td>
<td>Glove and stocking</td>
<td>2</td>
<td>Severe</td>
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<td>15</td>
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<td>SL</td>
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<td>1 × type II</td>
<td>750</td>
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<tr>
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<td>48/F</td>
<td>LL</td>
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<td>Glove and stocking</td>
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<td>Intraneural</td>
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<td>SL</td>
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<td>8.21</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>17</td>
<td>43/F</td>
<td>LL</td>
<td>7.5</td>
<td>Glove and stocking</td>
<td>0.5</td>
<td>Severe</td>
<td>No bacilli seen</td>
<td>7</td>
<td>3.84</td>
<td>3.84</td>
<td>5.76</td>
<td>Mild</td>
<td>5 × type II</td>
<td>11250</td>
</tr>
</tbody>
</table>

RFT, released from treatment; n.p., nerve biopsy not performed; TT, tactile threshold at the dorsum of feet (number corresponds to a logarithmic function of the equivalent forces, grams); SL, sensory loss; CC, cumulative amount of corticosteroids.
second group \((n = 5)\) of patients with mononeuropathy or multiple mononeuropathy. The IENFs were significantly better preserved in controls than in either patient group \((P < 0.001,\) Mann–Whitney test). When the two groups of patients were compared, significantly less IENFs were present in the glove and stocking group \((P = 0.03)\). In this group, almost a total absence of IENFs was noticed in skin specimens of 11 patients, while IENFs were well preserved in one case (patient number 5 who had pain only in her palms and soles). IENF densities of all patients and controls are compiled in Figure 2.
No correlation was found between the IENF counts and patient age or gender ($P = 0.678$, $P = 0.984$, respectively). There was, however, a statistically significant negative correlation between the IENF count and the number of type I or type II reactions ($P < 0.001$, ANOVA): the more reactions patients had the fewer IENFs were found in skin specimens. There was also a growing tendency of patients with recurring reactions to experience more severe pain, even though the statistical significance was not reached ($P = 0.72$).

A sural nerve biopsy was performed in nine patients, all of whom had palpably thickened nerves. There was clear evidence of inflammation in nine nerve biopsy specimens. In eight biopsy specimens the perineurium was thickened while in one there was inflammation and lamination of the perineurium indicating ongoing intraneural inflammation. Scanty acid-fast bacilli were detected in five biopsy specimens. In two cases inflammatory activity was found even in the nerves with abundant co-existing fibrosis. Lymphocytes were the predominant inflammatory cell type in seven biopsy specimens. In this study with a limited number of patients, no statistical significances were found in the nerve biopsy findings between the different subgroups of leprosy. The amount of inflammation seen in the nerves did not correlate with IENF numbers.

Discussion

This study corroborated previous findings of the existence of chronic disturbing neuropathic pain in a subgroup of treated leprosy patients.\textsuperscript{2,14} Pain was predominantly of continuous burning type; lancinating pain was absent. Glove and stocking distribution was most common in our patients. In addition to pain, paresthesia was prevalent, and the intensity of these two symptoms was in concordance in most cases. Sleep was interrupted due to pain, and most patients used pain medications regularly. However, there are no controlled studies on the efficacy of simple analgesics on chronic neuropathic pain. The choice of treatment in these patients reflects the local availability, cost and awareness of pharmacotherapy of neuropathic pain. Tricyclic antidepressants and several antiepileptic drugs have good evidence of efficacy in various neuropathic pain states,\textsuperscript{15} but to date there are no studies of their use in leprosy-related neuropathic pain.\textsuperscript{16}

In our patients, no signs of hyperalgesia or allodynia were found. The possible explanation could be silent inflammation and slow but complete destruction of nerves. It has been suggested that hyperalgesia and allodynia are typical in states with well preserved and irritated peripheral sensory fibres which are overactive and cause central sensitisation.\textsuperscript{17} In diseases such as leprosy, with profound loss of peripheral nerve fibres, allodynia caused by overactive peripheral fibres is an unlikely phenomenon.

PGP 9.5 immunostaining of skin biopsies has been used to quantify IENF density and its alterations to document the presence of peripheral neuropathy.\textsuperscript{18,19} Previous studies have demonstrated the usefulness of cutaneous nerve evaluation in SFN of various origins.\textsuperscript{20,13} The existence of SFN in leprosy patients has previously been shown\textsuperscript{21,22} but until now it has not been demonstrated histopathologically using IENF assessment. The skin biopsies were taken from standard sites, i.e. ankle, because the reference values have not been published from other parts of the body. In forthcoming studies punch biopsies may be needed to take both from the painful area and the standard location.

One of the possible reasons for pain in treated leprosy patients could be an ongoing chronic inflammation in and around the nerves. Inflammation along nerve trunks has been
shown to produce ectopic activity in nerves. This may lead to prolonged afferent barrage to the dorsal horn causing central sensitisation, and finally chronic neuropathic pain. It is noteworthy that most of our patients had some nerve tenderness and that the nerve biopsies showed evidence of ongoing inflammation. Further studies should investigate the molecular mechanisms underlying this ongoing inflammation and cellular activation. It is possible that \textit{M. leprae} antigens persist in nerves, possibly inside Schwann cells and that these are being presented to the immune system. A previous study on nerve biopsies from leprosy patients with Type I reactions showed that \textit{M. leprae} antigens were detectable in reactional nerves. These data reinforce the observation that clinical and pathological processes can occur in leprosy patients long after multi-drug therapy. In a few patients, vasculitis of the small epineural vessels, precipitated by persisting mycobacterial antigen, may lead to ischemic injury of the nerves and cause painful neuropathy. In our patients, none had evidence of vasculitis in sural nerve biopsy specimens.

In addition to present inflammatory conditions, the burden of past episodes of neuritis may be a source of pathologic and aberrant activity of peripheral nerves. Acid fast bacilli were detected in five nerve biopsies. Patients had completed MDT from 1 to 11.5 years previously. This raises the possibility that even in this small set of patients with nerve pathology bacteria are persisting in the nerve. We have no way of knowing whether these bacilli were viable. We also do not know whether the patients were compliant with their treatment. For patients treated many years previously re-infection is a possibility. However, Shetty \textit{et al.} have shown that \textit{M. leprae} can be recovered from the nerves of patients who have been treated with MDT. Porichha has also shown that in patients with post-treatment neuritis there is evidence of active disease. This emphasises the long-term pathology occurring in the nerves of leprosy patients.

There are some important methodological limitations in our study. Firstly, there was no suitable control group. Including a control group with patients who did not have neuropathic pain and who were matched for the type and duration of leprosy would have given valuable information on the role of SFN in leprosy-related painful neuropathy. Secondly, control skin biopsies were taken from Finnish patients. Even though the differences in IENF density in healthy individuals are unlikely among ethnic groups, it would have been appropriate to include an Indian control group. Thirdly, tools used in the assessment of thermal sensation were not validated. The Swiss Thermal Sensation Tester has been widely distributed among leprosy field workers but there is no available data on its validation.

Despite the limitations, we found clear evidence of ongoing inflammation in biopsy specimens of treated leprosy patients. In these patients an obvious SFN due to leprosy was also verified histopathologically. A larger cross-sectional study of a population of treated patients with an appropriate control group is needed to define the extent of the problem. It would also enable the identification of possible pathophysiological mechanisms more accurately. It is presumable that the mechanisms of neuropathic pain vary between subtypes of leprosy. A larger study would also be able to address other important issues such as the impact that ongoing neuropathic pain has on the quality of life of these patients and whether it causes depression. Further studies are also needed to develop protocols for the management of neuropathic pain.
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Contributors

The project was initiated and designed by Aki Hietaharju with help from Diana NJ Lockwood, Sujai Suneetha, Maija Haanpää, and Hannu Haapasalo. Patient data was collected by Caroline Lund and Sujai Suneetha. Intraepidermal nerve counting was done by Mika Koskinen, and examination of sural nerve biopsy specimens by Sujai Suneetha. Data analysis and write up was done by Mika Koskinen, Caroline Lund, Diana NJ Lockwood, and Aki Hietaharju. Aki Hietaharju is the guarantor for this paper.

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