Chronic pain in pachyonychia congenita: evidence for neuropathic origin

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Summary

Background Pachyonychia congenita (PC) is a rare autosomal dominant skin disease, with chronic pain being the most prominent complaint. Histological studies showing alterations in sensory innervation, along with reports on alterations in mechanical sensitivity, suggest that PC may be a form of neuropathy.

Objectives Here, for the first time, we aim to evaluate systematically the sensory function of patients with PC vs. controls, in order to investigate the pathophysiology of PC.

Methods Patients (n = 62) and controls (n = 45) completed the McGill and Douleur Neuropathique-4 (DN4) questionnaires. Sensory testing included detection and pain thresholds, pathological sensations, conditioned pain modulation (CPM) and temporal summation of pain.

Results A moderate-to-severe chronic pain in the feet, throbbing and stabbing in quality, was highly prevalent among patients with PC (86%) and was especially debilitating during weight bearing. In addition, the majority of patients had a DN4 score ≥ 4 (62%), static allodynia (55%) and tingling (53%) in the feet. Compared with controls, patients with PC exhibited thermal and mechanical hypoaesthesia and mechanical hyperalgesia in the feet. CPM was reduced among the patients, and was associated with more enhanced mechanical hyperalgesia in the feet. The specific gene and nature of the causative mutation did not affect any of these features.

Conclusions Although thermal and mechanical hypoaesthesia may result from thicker skin, its presentation in painful regions, along with mechanical hyperalgesia and allodynia, point towards the possibility of neuropathic changes occurring in PC. The clinical features and DN4 scores support this possibility and therefore neuropathic pain medications may be beneficial for patients with PC.

What’s already known about this topic?
- Chronic pain is the most prominent and debilitating complaint in pachyonychia congenita (PC).
- The origin of this pain has not been established and hence an appropriate intervention is also lacking.
- Histological studies have found alterations in sensory innervation.

What does this study add?
- Systemic sensory testing revealed hypoaesthesia along with mechanical hyperalgesia and allodynia (pain resulting from a nonpainful stimulus) in the painful body regions.
Pachyonychia congenita (PC) is an autosomal dominant skin disease caused by a mutation in one of five genes encoding different keratins, i.e. KRT6A (K6a), KRT6B (K6b), KRT6C (K6c), KRT16 (K16) or KRT17 (K17). These keratins are expressed in keratinocytes of the nail, palmar plantar skin, mucosa and hair, leading to clinical manifestations at these sites.  

Clinically, PC features a triad of nail dystrophy, plantar keratoderma and plantar pain presenting at birth or in early childhood. The pain is severe and debilitating, especially on weight-bearing areas, and is a significant limiting factor with regard to activity in daily living. Plantar pain in particular has the most profound impact on quality of life. Other common clinical manifestations include cysts, follicular hyperkeratosis, oral leucokeratosis, hyperhidrosis and palmar keratoderma. The pain reported by patients with PC has not been formally characterized and therefore its pathophysiology remains elusive. As no specific treatment or cure is known for PC, therapy is generally directed towards symptomatic improvement. A systematic evaluation of the chronic pain and sensory profile of patients with PC is necessary to delineate the pathophysiology of the pain and design efficient pain management strategies.

To the best of our knowledge, only two studies conducted sensory testing among patients with PC. Wallis et al. reported alterations in mechanical detection and pain thresholds in the feet of patients with PC, yet the nature of these alterations was not reported, probably owing to the lack of a control group. Pan et al. reported lower pressure pain thresholds in the affected plantar skin of 10 patients with PC compared with intact skin, along with less sweat gland innervation and Meissner corpuscles. They also reported more Merkel cells and blood vessels in the affected skin of patients with PC as revealed by skin biopsies. Consequently, the function of non-nociceptive nerve fibres has not been evaluated in PC; however, the function of nociceptive fibres has been evaluated based on a small sample size and requires additional testing. Furthermore, pain modulation capacity of patients with PC has not been previously evaluated and is essential for the understanding of chronic pain pathology.

Owing to the dearth of information regarding the sensory profile of patients with PC and the possibility that such information can shed light on the pathophysiology of PC and lead to better pain management, the aims of this study were to evaluate, among patients with PC vs. controls, (i) the somatosensory function and pain modulation capacity and (ii) the association between these factors and the chronic pain characteristics.

**Materials and methods**

**Participants**

Overall, 107 individuals participated and comprised the following two groups: (i) 62 individuals diagnosed with genetically confirmed PC (PC group; 29 men and 33 women, average age 44.8 ± 16.4 years) and (ii) 45 sex- and agematched healthy controls (HCs) (HC group; 18 men and 27 women, average age 39.2 ± 15.5 years). Patients with PC who had mutations in KRT6A or KRT16 were recruited through the International Pachyonychia Congenita Research Registry. Healthy subjects were recruited from among employees of the Tel-Aviv Medical Center and from members of the PC Project personnel.

The study was approved by the Western Institutional Review Board (WIRB 20111060). Written informed consent was obtained from all subjects, according to the Declaration of Helsinki guidelines after they received a full explanation of the study protocol and goals.

**Equipment**

**Thermal stimulator**

Heat stimuli were delivered using a Peltier-based computerized thermal stimulator (TSA II, Medoc Ltd., Ramat-Ishay, Israel) with a contact probe (3 × 3 cm). The probe was attached to the testing site by means of a Velcro band. In cases where the testing site was too large, the examiner held the probe.

**Water bath**

Cold stimuli were delivered using a 4-L cylindrical water bath filled with ice water, which was maintained at a temperature of 10 °C.

**Pressure algometer**

Pressure stimuli were delivered, using a handheld pressure algometer (Algometer type II, Somedic Sales AB, Sösdala, Sweden) with a 1-cm diameter contact probe, which was pressed...
against the skin. The exertion of a constantly increasing rate of pressure was monitored on the display.

**Semmes–Weinstein monofilaments**

Mechanical stimuli were applied using Semmes–Weinstein monofilaments (North Coast Medical Inc., Morgan Hill, CA, U.S.A.) comprising 20 calibrated monofilaments, with sizes ranging from 1.65 g to 6.65 g, inducing a calibrated force ranging from 0.008 g to 300 g, respectively.

**Visual analogue scale**

Chronic and experimental pain intensity was measured using a visual analogue scale (VAS) consisting of a horizontal red bar (the visual side) exposed to the subject, while the side facing the experimenter displayed an analogue scale with values between 0 = 'no pain sensation' and 10 = 'the most intense pain sensation imaginable'. The subject moved the inner slider according to their pain experience.

**Sensory testing**

**Sensory thresholds**

Sensory detection thresholds were measured to evaluate the sensitivity of the nervous system to innocuous stimuli and to evaluate conduction in C fibres (warmth threshold), A-delta fibres (cold threshold) and A-beta fibres (touch threshold). Warm and cold detection thresholds were measured using the computerized thermal stimulator. The mechanical detection threshold was measured using the Semmes–Weinstein monofilaments. Pain thresholds were measured in order to evaluate the sensitivity of the nervous system to noxious stimuli and to evaluate conduction in nociceptive C fibres and A-delta fibres. Heat pain threshold (HPT) was measured using the computerized thermal stimulator. Pressure pain threshold (PPT) was measured using the pressure algometer. All thresholds were measured in the feet (painful regions) and forearms (pain-free regions) using the method of limits, in which a series of stimuli is presented at a gradually increasing magnitude and participants are instructed to report on the tested sensation.

**Conditioned pain modulation**

Conditioned pain modulation (CPM) is an experimental paradigm representing the spinal-bulbar-spinal inhibitory circuit termed 'diffuse noxious inhibitory control' (DNIC), mediated by the brainstem subnucleus reticularis dorsalis. DNIC refers to the inhibition of pain by neurons outside the area from which the nociceptive input originated and it was measured as an index of pain-inhibition capacity. CPM was measured by administering a noxious stimulus to one arm (the test stimulus) and evaluating its perceived intensity alone and in the presence of another noxious stimulus applied to the contralateral hand (conditioning stimulus).

**Temporal summation of pain**

Temporal summation of pain (TSP) refers to a phenomenon in which perceived pain gradually increases in response to repeated/constant, moderately painful stimuli of fixed intensity. TSP is centrally mediated by frequency-dependent increments in spinal nociceptive neurons and was measured as an index of nociceptive excitability. Subjects immersed their hand (up to the wrist line) in a cold water bath (10 °C) for 30 s and rated their pain at immersion, after 15 s and at the end of hand immersion, using the VAS. The magnitude of TSP was calculated by subtracting the last VAS rating from the first.

**Abnormal sensations**

Allodynia is pain evoked by a normally non-noxious stimulus, associated with hyperexcitability of the nervous system and often present in patients with neuropathic pain. Static and dynamic allodynia were measured using monofilaments. Hyperpathia is the emergence of a sudden strong painful sensation, which persists after stimulation is turned off, and is also associated with hyperreactivity of the pain system, especially in neuropathic pain. Hyperpathia was measured with the thermal stimulator.

**Questionnaires**

**McGill pain questionnaire**

Chronic pain was quantified using the short form of the McGill pain questionnaire (MPQ) and VAS.

**Douleur Neuropathique-4 questionnaire**

The patients with chronic pain completed the Douleur Neuropathique-4 (DN4) questionnaire, a clinician-administered questionnaire developed and validated for the purpose of discriminating neuropathic pain from non-neuropathic pain.

**Experimental design**

Testing took place in a quiet room with ambient temperature that was maintained at a constant level. Subjects were examined during a single testing session, which was preceded by a training session. Prior to testing, each patient with PC was interviewed regarding the location of painful and pain-free body regions and the chronic-pain characteristics (intensity, duration, quality, ameliorating and aggravating factors, spontaneous or evoked abnormal sensation in painful regions, etc.). The patients rated chronic pain on a VAS and completed the MPQ. Then, sensory testing commenced and included the evaluation of abnormal sensations and measurement of thresholds (in the pain-free volar surface of the forearm and in the painful distal third of the plantar surface of the foot), CPM and TSP (both tested in the forearms and hands only), in random order. If blisters and/or bandages prevented the
examiner from testing the designated foot region, testing was carried out on an adjacent region (the mid-third of the foot in most cases). PPT was specifically measured in the foot, on account of pain during weight bearing/walking. The testing of controls was performed at comparable body locations. The order of the testing with thermal and mechanical stimuli was also randomized.

Statistical analysis
Data were processed using SPSS version 23 statistics software (IBM, Armonk, NY, U.S.A.). Between-group (patients/controls, K6a/K16) comparisons were conducted using t-tests (age, time durations, pain intensity, detection/pain thresholds, CPM), the Mann–Whitney U-test (DN4) and $\chi^2$-tests (sex, pain at rest/weight bearing, abnormal sensations). Repeated-measure analysis of variance (RANOVA) was used to analyse the time trend and group effect on TSP. Correlations between pairs of variables were calculated using Pearson’s or Spearman’s $r$. Multiple testings were addressed by using the false discovery rate procedure that controls for the expected proportion of falsely rejected hypotheses, which is the desirable control against errors originating from multiplicity. A two-sided $P$-value < 0.05 was considered statistically significant.

Results

Characteristics of the study groups and of the chronic pain
Table 1 describes the study group and chronic pain characteristics. Age and sex distributions were similar across groups. Most of the patients with PC (86%) reported being affected by chronic pain, localized mostly in the palmar and plantar regions. Pain intensity was moderate-to-severe ranging from 2.7 ± 2.3 (at its least) to 8.7 ± 1.3 (at its worst). The two mutation PC subtypes (K6a/K16) did not differ in chronic pain intensity. The quality of chronic pain based on the MPQ was mostly aching (87%), throbbing (83%), sharp (83%), stabbing (79%) and shooting (79%). The most frequent affective pain descriptor was ‘tiring’. Almost all of the patients with chronic pain (93%) reported that the pain is felt during weight bearing and only a minority of patients reported pain during rest. Of the 53 patients with chronic pain, 29 (55%) reported taking analgesic medications regularly and 17 (32%) reported that these medications efficiently reduced the pain. Figure 1 presents the abnormal sensations in the painful body regions, with allodynia, tingling and electric-shock-like sensations being the most frequent.

Sensory testing
Detection and pain thresholds
Table 2 presents the sensory thresholds. Patients with PC had higher thresholds than controls for thermal sensation in both the upper and lower limbs and also had a higher touch detection threshold in the lower limbs, suggesting thermal and mechanical hypeaesthesia. The two groups did not differ in HPT; however, patients with PC had a lower PPT in the lower limb, which can be indicative of mechanical hyperalgesia.

Table 1  Characteristics of the study groups and the chronic pain of pachyonychia congenita (PC)

<table>
<thead>
<tr>
<th></th>
<th>PC (n = 62)</th>
<th>Controls (n = 45)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>44.8 (16.4)</td>
<td>39.2 (15.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>Sex (men/women)</td>
<td>29/33</td>
<td>18/27</td>
<td>0.048</td>
</tr>
<tr>
<td>Gene mutation (K6a/16), n</td>
<td>29/33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean duration of PC, years (SD)</td>
<td>42.8 (17.8)</td>
<td>33.6 (22.3)</td>
<td></td>
</tr>
<tr>
<td>Prevalence of chronic pain, n (%)</td>
<td>53 (86)</td>
<td>62 (57)</td>
<td></td>
</tr>
<tr>
<td>Mean duration of chronic pain, years (SD)</td>
<td>33.6 (22.3)</td>
<td>33.6 (22.3)</td>
<td></td>
</tr>
<tr>
<td>Mean pain intensity by VAS score (range 0–10) (SD)</td>
<td>5.7 (1.6)</td>
<td>5.7 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Mean pain intensity by MPQ score (SD)</td>
<td>22.2 (10.3)</td>
<td>22.2 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Pain during rest, n (%)a</td>
<td>9 (17)</td>
<td>9 (17)</td>
<td></td>
</tr>
<tr>
<td>Pain during weight bearing, n (%)a</td>
<td>50 (94)</td>
<td>50 (94)</td>
<td></td>
</tr>
<tr>
<td>Mean DN4 score (range 0–10) (SD)</td>
<td>4.0 (2.6)</td>
<td>4.0 (2.6)</td>
<td></td>
</tr>
</tbody>
</table>

VAS, visual analogue scale; MPQ, McGill pain questionnaire; DN4, Douleur Neuropathique-4 questionnaire. P-values are based on comparison between the groups (two-tailed). aCalculation taken from the 53 patients with chronic pain.

Fig 1. Pathological sensations among patients with pachyonychia congenita. Static allodynia, tingling and electric-shock-like sensations were highly prevalent (95% confidence intervals of 42–67%, 39–68% and 32–60%, respectively), whereas dynamic allodynia, paradoxical pain and hyperpathia were less frequent (95% confidence intervals of 11–44%, 5–37% and 2–32%, respectively).
Importantly, there were no differences in any of the thresholds tested between the two PC gene subtypes (not shown).

### Pain modulation

Patients with PC had a significantly lower ability to inhibit pain than controls ($P < 0.01$) (Fig. 2, left bars). Pain ratings decreased from $4.43 \pm 3.8$ to $3.8 \pm 2$ among patients with PC ($\Delta = -0.75$ VAS units) and from $4.87 \pm 1.7$ to $3.1 \pm 1.5$ among controls ($\Delta = -1.65$). Both groups exhibited similar TSP as indicated by a significant effect of time $[F(2,164) = 163.5, P < 0.001]$ but lack of group effect $[F(1,82) = 3.0, P = 0.087]$ and group by time interaction $[F(2,164) = 0.20, P = 0.81]$ (Fig. 2, right bars). Pain ratings increased from $1.94 \pm 1.8$ to $4.9 \pm 3$ among patients with PC ($\Delta = 3.0$ VAS units) and from $2.98 \pm 2.0$ to $5.9 \pm 2.5$ among controls ($\Delta = 2.9$). No differences were observed in CPM or TSP between the two PC gene subtypes.

### Correlations between variables

Neither pain intensity nor DN4 score correlated significantly with any of the sensory testing (Table 3). A longer chronic pain duration was associated with less intense pain, higher thermal detection thresholds (i.e. more pronounced hypoesthesia) but higher PPT (i.e. less pronounced hyperalgesia). PPT correlated negatively with CPM; patients with more enhanced mechanical hyperalgesia in the foot had less efficient CPM.

### Douleur Neuropathique-4 questionnaire results

The average DN4 score was $4.0 \pm 2.6$ (ranging from 0 to 10) (Table 1). The majority of patients who had PC with chronic pain (62%) had a DN4 score $\geq 4$, suggesting a positive diagnosis for neuropathic pain. Although sensory testing was similar for patients with a DN4 score above or below a score of 4, patients with a DN4 score greater than 4 exhibited significantly higher rates of tingling ($18$ of $33$ vs. eight of $28$, $P < 0.05$) and numbness ($12$ of $33$ vs. three of $28$, $P < 0.05$), and higher chronic pain intensity (MPQ $25.1 \pm 9$ vs. $17.9 \pm 9$, $P < 0.05$) than patients with a score below 4.

### Discussion

The results show that 86% of patients with PC report chronic pain that was especially prominent in the feet and during weight bearing. In order to ascertain the nature and origin of the pain, the chronic pain and sensory profile were characterized and the diagnostic DN4 questionnaire was completed.

The majority of patients reported moderate-to-strong pain of an aching quality, a feature more typical in pain of musculoskeletal origin.\(^{22}\) Yet, at the same time, the descriptors ‘throbbing’, ‘sharp’ and ‘shooting’ were similarly frequent, which are qualities that are characteristic of neuropathic pain.\(^{22,28,29}\) Almost all patients with chronic pain reported that the pain was felt mainly during weight bearing, a complaint not typical of neuropathic pain in which pain is usually spontaneous but may worsen during activity.\(^{32}\) Some patients with PC also reported that the pain is evoked or exacerbated when the affected skin is wet, a complaint that seems to be specific to PC.

The patients with PC exhibited increased thermal thresholds in both the feet and forearms compared with controls, indicating reduced thermal sensitivity (hypoesthesia). The thick skin of the feet resulting from hyperkeratosis may be the reason for the thermal hypoesthesia in the feet, as more stimulation energy is required in order to activate the cutaneous

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Table 2: Average (SD) of sensory and pain thresholds among the study groups

<table>
<thead>
<tr>
<th></th>
<th>PC (n = 61)</th>
<th>Controls (n = 45)</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upper limbs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warm detection</td>
<td>34.9 (0.9)</td>
<td>34.5 (1.1)</td>
<td>$&lt; 0.05$</td>
</tr>
<tr>
<td>threshold, °C</td>
<td>Cold detection</td>
<td>29.9 (1.3)</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>threshold, °C</td>
<td>Touch detection</td>
<td>3.3 (0.5)</td>
<td>0.6</td>
</tr>
<tr>
<td>threshold, gf</td>
<td>Heat pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>threshold, °C</td>
<td>42.9 (3.2)</td>
<td>43.5 (3.0)</td>
<td>0.28</td>
</tr>
<tr>
<td>Lower limbs</td>
<td>42.4 (4.5)</td>
<td>39.5 (3.3)</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Warm detection</td>
<td>25.8 (4.3)</td>
<td>29.2 (1.4)</td>
<td>$&lt; 0.0001$</td>
</tr>
<tr>
<td>threshold, °C</td>
<td>Cold detection</td>
<td>3.6 (0.5)</td>
<td>$&lt; 0.05$</td>
</tr>
<tr>
<td>threshold, °C</td>
<td>Touch detection</td>
<td>47.4 (2.9)</td>
<td>0.11</td>
</tr>
<tr>
<td>threshold, gf</td>
<td>Heat pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>threshold, °C</td>
<td>195.3 (138)</td>
<td>429.6 (211)</td>
<td>$&lt; 0.0001$</td>
</tr>
<tr>
<td>Pressure pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>threshold, kPa</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PC, pachyonychia congenita; kPa, kilopascal; gf, gram force.
P-value are based comparison between the groups (two-tailed).

Fig. 2. Pain modulation among patients with pachyonychia congenita (PC). The magnitude of conditioned pain modulation (Δ visual analogue scale (VAS)) was significantly lower among patients with PC compared with healthy controls ($***P < 0.01$). The magnitude of temporal summation of pain (TSP) (Δ VAS) was similar across groups. Bars denote group mean ± SEM.

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Table 3  Correlation coefficients within the pachyonychia congenita (PC) group

<table>
<thead>
<tr>
<th>Pain duration</th>
<th>PC duration</th>
<th>Pain intensity</th>
<th>DN4</th>
<th>Age</th>
<th>WDT</th>
<th>CDT</th>
<th>MDT</th>
<th>HPT</th>
<th>PPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC duration</td>
<td>0.65 (^a) (0.39–0.81)</td>
<td>-0.44 (^b) (-0.61 to -0.27)</td>
<td>0.03</td>
<td>0.09</td>
<td>0.08</td>
<td>0.22</td>
<td>0.32 (^d) (0.30-0.32)</td>
<td>0.00</td>
<td>-0.18</td>
</tr>
<tr>
<td>Pain intensity</td>
<td>0.019</td>
<td>0.019</td>
<td>0.03</td>
<td>0.07</td>
<td>0.22</td>
<td>0.15</td>
<td>0.22</td>
<td>0.00</td>
<td>-0.18</td>
</tr>
<tr>
<td>DN4</td>
<td>0.65 (^a) (0.35–0.83)</td>
<td>0.98 (^a) (0.84–0.97)</td>
<td>-0.10</td>
<td>0.03</td>
<td>0.019</td>
<td>0.019</td>
<td>0.03</td>
<td>0.07</td>
<td>0.22</td>
</tr>
<tr>
<td>Age</td>
<td>0.36 (^a) (0.02–0.67)</td>
<td>0.02</td>
<td>0.22</td>
<td>0.07</td>
<td>0.15</td>
<td>0.22</td>
<td>0.00</td>
<td>-0.18</td>
<td>-0.55 (^a) (-0.69 to -0.29)</td>
</tr>
<tr>
<td>WDT</td>
<td>0.49 (^d) (-0.68 to -0.13)</td>
<td>0.32 (^d) (0.30-0.32)</td>
<td>-0.00</td>
<td>-0.18</td>
<td>-0.55 (^a) (-0.69 to -0.29)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDT</td>
<td>0.65 (^a) (0.29–0.83)</td>
<td>0.49 (^b) (-0.29–0.83)</td>
<td>0.01</td>
<td>0.22</td>
<td>0.019</td>
<td>0.019</td>
<td>0.03</td>
<td>0.07</td>
<td>0.22</td>
</tr>
<tr>
<td>MDT</td>
<td>0.019</td>
<td>0.019</td>
<td>0.03</td>
<td>0.07</td>
<td>0.22</td>
<td>0.15</td>
<td>0.22</td>
<td>0.00</td>
<td>-0.18</td>
</tr>
<tr>
<td>HPT</td>
<td>0.34 (^a) (0.10–0.93)</td>
<td>0.33 (^d) (0.30-0.32)</td>
<td>-0.07</td>
<td>0.25</td>
<td>0.04</td>
<td>0.04</td>
<td>0.05</td>
<td>0.11</td>
<td>0.04</td>
</tr>
<tr>
<td>PPT</td>
<td>0.65 (^a) (0.29–0.83)</td>
<td>0.49 (^b) (-0.29–0.83)</td>
<td>0.01</td>
<td>0.22</td>
<td>0.019</td>
<td>0.019</td>
<td>0.03</td>
<td>0.07</td>
<td>0.22</td>
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<tr>
<td>CPM</td>
<td>0.31 (^d) (0.10–0.93)</td>
<td>0.21</td>
<td>0.21</td>
<td>-0.07</td>
<td>0.25</td>
<td>0.04</td>
<td>0.04</td>
<td>0.11</td>
<td>0.04</td>
</tr>
<tr>
<td>TSP</td>
<td>0.64 (^a) (0.29–0.83)</td>
<td>0.49 (^b) (-0.29–0.83)</td>
<td>0.01</td>
<td>0.22</td>
<td>0.019</td>
<td>0.019</td>
<td>0.03</td>
<td>0.07</td>
<td>0.22</td>
</tr>
</tbody>
</table>

DN4, Douleur Neuropathique-4; WDT, warm detection threshold; CDT, cold detection threshold; MDT, mechanical detection threshold; HPT, heat pain threshold; PPT, pressure pain threshold; CPM, conditioned pain modulation; TSP, temporal summation of pain. \(^a\)P < 0.0001; \(^b\)P < 0.01; \(^c\)P < 0.05; \(^d\)P = 0.055–0.065 (two-tailed). Values in parentheses are 95% confidence intervals for significant standardized coefficients.
Chronic pain in pachyonychia congenita, S. Brill

Chronic pain in pachyonychia congenita (PC), which is pain during weight bearing, may contribute to one of the major features of the chronic pain in PC (and thus contributed to its emergence) or resulted from it. Although the magnitude of chronic pain did not correlate with the mechanical hyperalgesia, the less efficient the nociceptors. The normal temporal summation threshold indicates that patients with PC did not present generalized hyperexcitability. However, the patients did have reduced CPM compared with controls, which is indicative of dysfunctional pain inhibition capacity. Such a dysfunction is common in patients with chronic pain of various aetiologies, including neuropathic pain. It is not clear whether deficient CPM preceded the development of the chronic pain in PC (and thus contributed to its emergence) or resulted from it. Although the magnitude of CPM did not correlate with either the intensity or the duration of chronic pain, it did correlate with the mechanical hyperalgesia in the feet; the enhanced mechanical hyperalgesia, the less efficient the CPM. This correlation suggests that the reduced ability to inhibit pain may contribute to one of the major features of the chronic pain in PC, which is pain during weight bearing.

Along with hyperalgesia, allodynia, which was highly prevalent among the patients with PC, also indicates sensitization and is often observed in neuropathic pain. The presence of static allodynia in particular, which is mediated by unmyelinated C fibres, suggests that pain in PC is associated with nociceptive fibre sensitization. The patients with PC exhibited several additional ‘positive signs’, which are characteristic of neuropathic pain including tingling and electric-shock-like sensations. Paradoxical sensations and hyperpathia, revealed herein during thermal testing, have also been reported among patients with neuropathic pain, although these features are less frequent than allodynia.

Using the DN4 questionnaire, a score of 4 is the cut-off value for the diagnosis of neuropathic pain, as recently validated in diabetic polyneuropathy, back pain and peripheral neuropathies, for example. About 62% of patients with PC had a DN4 score ≥4, which is in agreement with the study by Wallis et al., which used a different diagnostic tool (pain-DETECT). Interestingly, sensory testing was similar among patients with a DN4 score above or below a score of 4; however, those with a score below 4 showed somewhat reduced frequencies of tingling and less severe chronic pain.

Neuropathic pain develops as a result of lesions or disease affecting the peripheral or central somatosensory nervous system. Neuropathic pain may encompass a broad spectrum of signs and symptoms, and combinations of gain (positive signs) and loss (negative signs) of sensibility are shared across the major neuropathic pain syndromes, as also found herein. The ‘positive’ neuropathic symptoms that are characteristic of patients with PC included spontaneous electric-shock-like sensations and tingling, allodynia and mechanical hyperalgesia. The ‘negative’ neuropathic signs and symptoms included thermal and mechanical hypoesthesia, although spontaneous signs (e.g. numbness and weakness) were not frequent among patients with PC. The aforementioned signs, along with the pain complaints and the DN4 scores, all support the possibility that the chronic pain in PC is, at least partly, of neuropathic origin. This does not preclude the possibility that in some patients the pain is of nociceptive origin, or started as nociceptive, but with the progression of the disease, elements of the nervous system were also affected.

The mechanism of chronic pain in PC is still unclear. Pan et al. have recently found that painful PC-affected skin demonstrated multiple alterations, including increased density of Merkel cells and blood vessels and reduced numbers of Meissner corpuscles and densities of small unmyelinated nerve fibres compared with intact skin. These findings support the possibility that damage to peripheral nerve fibres may be involved in the mechanism of pain in PC. Damage to sensory nerve fibres can generate a chain of events leading to peripheral sensitization. The observed hyperalgesia and allodynia in the PC-affected regions in this study may well be manifestations of peripheral sensitization. In addition, changes in the function of ion channels, specifically that of transient receptor potential channels, may possibly contribute to peripheral sensitization in neuropathic conditions, and also in the case of PC, owing to their expression by keratinocytes. The events leading to peripheral sensitization often involve the activation of proinflammatory substances and as such were already introduced in association with PC pathology; keratinocytes from PC-affected skin might express higher levels of neurotrophic factors such as interleukin-18, which, in turn, can increase neuronal excitability. Peripheral sensitization can, in turn, lead to spontaneous and evoked pain in addition to hypersensitivity to painful stimuli as reported by patients with PC.
It should be pointed out that the aforementioned positive and negative signs and symptoms are suggestive, but not pathognomonic for neuropathic pain. These signs and symptoms fulfil two of three levels of certainty in the diagnosis of neuropathic pain, according to a recently revised grading system.22 The alterations in small unmyelinated nerve fibres in PC and the location of pain in the same regions seem to fulfil the possible neuropathic pain criteria. The presence of both negative and positive signs in the PC-affected regions (negative signs to a lesser extent than positive signs) partly fulfil the next level of certainty, i.e. probable neuropathic pain. The level ‘probable’ is suggested to be sufficient to initiate treatment according to neuropathic pain guidelines. The final level of certainty, i.e. definite neuropathic pain, requires an objective diagnostic test confirming the lesion/disease of the somatosensory nervous system.23 While the sensory testing herein and the skin biopsy firming the lesion/disease of the somatosensory nervous system are not taken such medications. They may also experience chronic pain other than neuropathic pain. Several limitations should be considered. Firstly, the patients were not assessed at the time of PC diagnosis and therefore the results represent both primary and secondary consequences of any peripheral pathology that may have initiated the pain. Secondly, some features of the patients with PC suggested that they may also experience chronic pain other than neuropathic pain. Thirdly, the analgesic medications taken by approximately half of the patients may have affected the results, although sensory testing of these patients was similar to those not taking such medications.

In summary, the clinical examination and the sensory testing support the possibility that the chronic pain reported in the PC-affected regions is, at least in part, of neuropathic origin. Medications aimed to reduce neuropathic pain may be useful for patients with PC. These may include, but are not restricted to, tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors and GABA receptor agonists.44

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References
