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Case Report

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A prospective case of postherpetic itch monitored by quantitative sensory testing for 1 year while undergoing 8% topical capsaicin treatments

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Abstract

Following reactivation of a latent ganglionic varicella zoster virus and skin eruption in the corresponding dermatome(s) ~20% of patients develop chronic postherpetic neuralgia. A subset of these patients develop severe and often intractable chronic postherpetic itch in the affected area. However, this is rarely studied and little is known about its epidemiology, pathogenesis, and management. In this case study we followed a patient with moderate to severe chronic postherpetic itch characterized by pure itch sensation, using standardized quantitative sensory testing and observed a profound loss-of-function for C-fibers, Aδ-fibers, and Aβ-fibers within the affected area. The testing was conducted before, during, and after 8% topical capsaicin treatments applied in 4 cycles (3 months apart) over the course of ~1 year. During this period the hypoesthesia gradually normalized, but heat hypoalgesia remained unchanged. The 8% topical capsaicin had a good and long lasting antipruritic effect eventually resulting in complete resolution of the itch in parallel with partial recovery of initial hypoesthesia, particularly for warmth and cold detection, likely unrelated to the treatments.

Keywords: Itch, Pruritus, Postherpetic neuralgia, Capsaicin, Neuropathic itch, c-fiber

Introduction

Chronic postherpetic itch (PHI) is a marginally studied sequela to shingles. After reactivation of a latent ganglionic varicella zoster virus and skin eruption in the dermatome(s) innervated by a corresponding sensory ganglion, ~20% of patients develop postherpetic neuralgia with advanced age as the major risk factor[1]. Of these patients an estimated 9%–35% experience chronic itch without any pain and about half of these experience itch at an intensity ≥ 4 on a visual analog scale ($VAS_{0-10\ cm}$)[2,3]. Despite this, PHI has only been sparsely researched and little is known about its pathogenesis[4,5]. On the basis of evidence from cases studies, PHI can be as disabling as pain, and is often intractable[2,4]. Although no controlled trials have been conducted specifically for PHI, case studies report partial efficacy of gabapentinoids, topical amitriptyline/ketamine, 8% topical capsaicin, pulsed radiofrequency treatment, and topical lidocaine[1,6–9], which is largely in line with treatment for postherpetic neuralgia and brachio-radial pruritus. Topically applied capsaicin causes strong depolarization of intraepidermal transient receptor potential vanilloid 1 (TRPV1)-positive pruritic and nociceptive C-fibers of the skin, which results in prolonged, reversible defunctionalization and deafferentation[10]. The Qutenza patch (Astellas Pharma Ltd, UK; Now Grünenthal GmbH, DE) provides topical delivery of 8% capsaicin and is approved for the treatment of nondiabetic peripheral neuropathic pain conditions[11]. Here we tested a PHI patient undergoing four 8% topical capsaicin treatment over a year with standardized quantitative sensory testing and showed, before treatment, a notable loss-of-function for C-fibers, Aδ-fibers, and Aβ-fibers in the affected area. Previously, we and others have found substantial but variable efficacy of 8% topical capsaicin in another neuropathic itch condition; notalgia paresthetica[12] and a recent proof-of-concept study showed a powerful antipruritic effect of 8% topical capsaicin on both evoked histaminergic and nonhistaminergic itch[13]. Correspondingly, this PHI patient had a good and prolonged antipruritic effect from this treatment, coinciding with reoccurence of normal sensory function.

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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A case of chronic postherpetic

A 58-year-old man diagnosed with chronic lymphatic leukemia, otherwise healthy, developed a severe eruption of herpes zoster in multiple dermatomes (T1–T2) on the right side of the upper back (**Fig. 1A**). In the affected area a vesicular, exuding, and later crust-forming lesion developed. Treatment of the varicella zoster virus with Aciclovir (800 mg tid) was initiated 1 day after the first signs

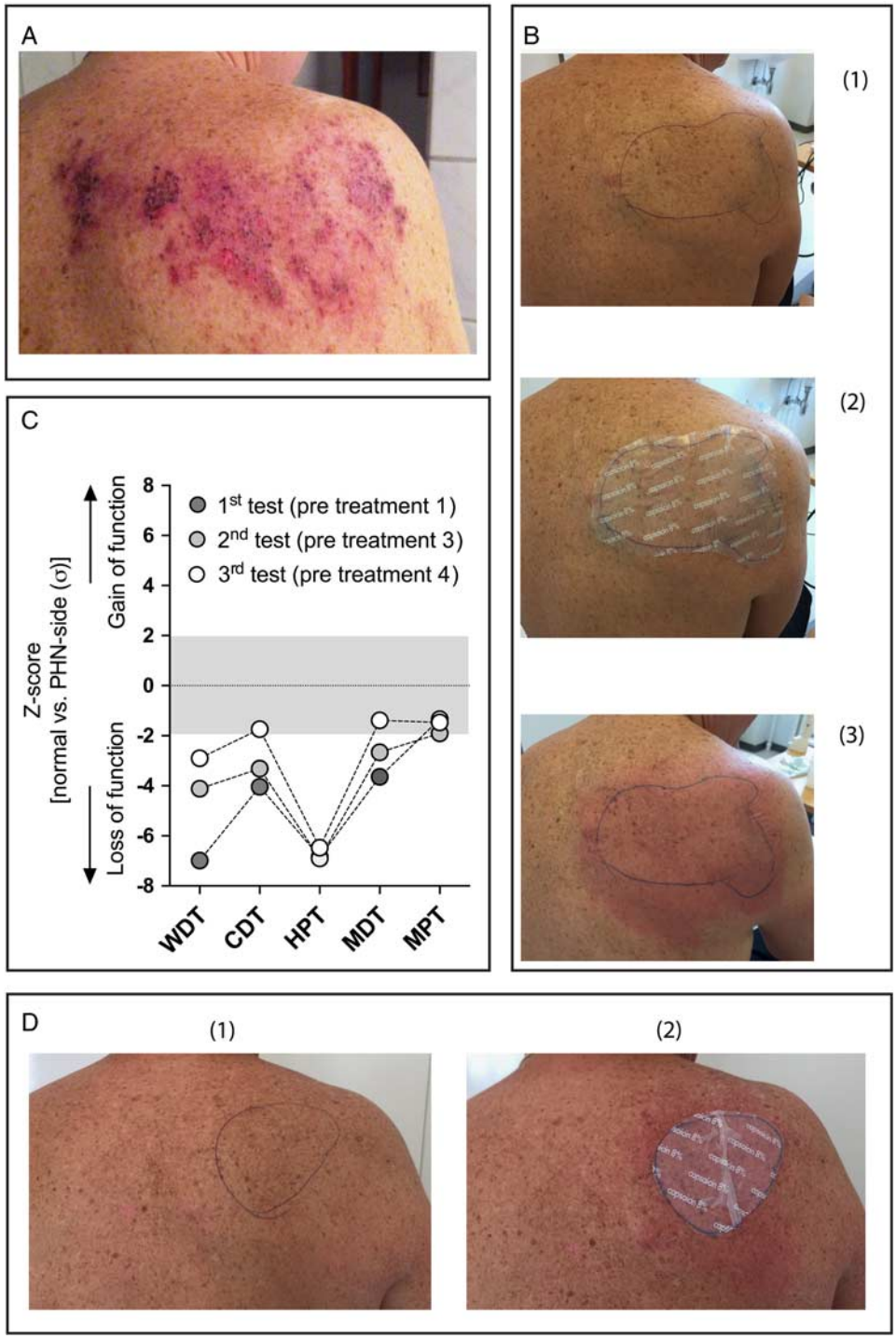

Figure 1. A, Active virus eruption. B, demarcation of the area of itch (1), application of an appropriately sized 8% capsaicin patch (2), axon-reflex-flare resulting from the capsaicin treatment immediately after patch removal (3). C, Sensory profile as assessed by quantitative sensory testing (notice the pronounced hypoesthesia of several parameters, which recovered during the 1 year and the contrasting stabile heat hypoalgesia). D, Demarcation of the area of itch (1) and fourth treatment (2) (see the diminished size of the area). CDT indicates cold detection threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; WDT, warmth detection threshold.

of rash and was effective in halting the outbreak and resolving most symptoms within 10 days. The skin eruption was not characterized by pain or paresthesia despite rather severe lesions (**Fig. 1A**). After 3–4 weeks when the skin eruption had been fully reversed, a constant, moderate to severe itch emerged corresponding to the eruption area. The patient reported being highly bothered by the itch primarily in the evenings and in the morning, while the intensity diminished somewhat during the day. Moreover, the patient reported an average itch intensity of 6 on a $VAS_{0–10}$ (0: "no itch," 10: "worst imaginable itch"). Initially

the patient did not experience significant touch-evoked itch (alloknesis) to, for example, wool fabrics, but this had developed at the second consultation. A treatment course with Gabapentin (300 mg bid) was ineffective in substantially reliving the itch. After 7 months with moderate to severe itch the patient was referred to our department and offered off-label treatment with 8% topical capsaicin. The patient consented to the 8% topical capsaicin treatment and the sensory testing as well as to the anonymized data being used for a case report. During the 1-hour capsaicin administration the patient experienced significant acute pain necessitating the use of Tramadol (50 mg, oral) during the following treatments, which made the treatment tolerable. The patient underwent 4 treatment cycles; 1 per 3 months (over ~1 year), of which the efficacy and temporal effect of the treatment gradually increased, that is, after the first treatment the patient reported 2 weeks of complete itch relief, whereafter the itch slowly remerged over the course of 2–3 months and approximated the initial level when next treatment was administered. The treatment effect increased progressively during the 4 cycles, so that the patient was free of itch for longer periods and that the reemergence of itch was less complete. The patient did not receive any regular treatment for chronic lymphatic leukemia or other prescription medications during the 8% topical capsaicin treatment period. Before the fourth capsaicin treatment the patient reported the average itch to be around 10% of the severity level reported at the initial treatment, that is, <1 ($VAS_{0–10}$). Furthermore he stated following the third treatment he was almost unbothered by itch except during exercise or when wearing certain synthetic fabrics. Approximately 9 months after the fourth treatment the last follow-up was performed and the patient reported being almost entirely free of itch, expect from mild itch occurring during strenuous exercise (spinning classes).

Methods: quantitative sensory testing

Immediately before capsaicin treatment no.: 1, 3, and 4, selected quantitative sensory testing (QST) parameters were assessed following the German Research Network on Neuropathic pain (DFNS) standardized protocol[14]. This was done to get a representative sensory profile before treatment initiation and to assess sensory implications of the repeated capsaicin administration. The testing always included both the affected and unaffected contralateral side (used as control) and the sensory parameters assessed were mechanical detection threshold (MDT, touch Aβ-fibers), mechanical pain threshold (MPT, Aδ-fibers), cold detection threshold (CDT, cold Aδ-fibers), warmth detection threshold (WDT, warmth C-fibers), and heat pain threshold (HPT, heat C-fibers). MDT was determined with a set of 20 calibrated Von Frey filaments (North Coast Medical, CA) with exerted forces ranging from 0.078 m N to 2.9 N was applied as ascending/descending series of stimuli. The patient was asked to report upon any sensation from the area. The MPT was evaluated using a set of 7 weight-calibrated pinprick stimulators (MRC Systems, Germany) with weights from 8 to 512 m N. The patient reported when a perception of "sharpness" or "pricking pain" was sensed during ascending/descending series of stimuli. CDT, WDT, and HPT were performed using a Medoc Q-sense (Medoc Ltd, Ramat Yishay, Israel) equipped with a 3×3 cm thermal probe. Ramping stimuli of 1°C/s were delivered from an adaptation temperature of 32°C until the patient identified the relevant threshold (first perception of cold, warmth or heat-induced pain) by pressing a button. Thresholds were assessed by the method of limits in triplicates (thermal) and quintuplicates (mechanical), and the differences expressed as z-scores ($[z = (\chi\text{-}\mu)/\sigma]$, hereby conveying the n difference of SD between the affected and nonaffected side). QST parameters were selected based on (1) being relevant to probing of superficial cutaneous fibres, (2) having access to the relevant equipment, and (3) being able to conduct the testing in 30–35 minutes. The sensory testing was always performed by the same investigator in a quiet examination room. The area of alloknesis was assessed by gentle radial strokes with a finger from outside and toward the suspect itching area.

Results: quantitative sensory testing

Immediately before each treatment the itch area was defined by lightly stroking the skin with the fingertips from well outside the relevant area and toward the center. The resultant area was marked, quantified, and treated (**Fig. 1B**, 1–3). Before the first capsaicin application the QST showed considerable tactile and thermal hypoesthesia as well as thermal hypoalgesia in the affected region compared with the contralateral side (**Fig. 1D**). WDT, CDT, HPT, and MDT were all reduced by >2 SDs in the herpes zoster eruption site. The only sensory modality relatively unaffected was MPT (ie, never differing >2 SDs) but it was still consistently higher in the site of the herpes zoster flare-up (average, 174.9 ± 111.2 mN) than in the contralateral site (average 100.8 ± 49.4 mN). Before the third and fourth capsaicin treatments normalization of hypoesthesia, but not hypoalgesia, was observed across the assessed parameters, in particular for CDT as well as MDT. Moreover, the WDT also showed signs of normalization, but never recovered to <2 SDs of the unaffected control area. Lastly, during the 4 treatment cycles the spatial extend of the itch/alloknesis area greatly diminished from ~280 cm^2, to 200 cm^2, to 140 cm^2, and to 65 cm^2 (**Fig. 1D**, 1–2) before the last treatment. The patient himself spontaneously reported experiencing a decrease in the area of itch at the fourth consultation before the area assessment.

Discussion

We here present the first long-term QST-based monitoring of a patient with PHI and report the observation of considerable sensory loss in the affected area with a tendency toward gradual recovery over the course of 1 year. Achieving satisfactory relief in patients suffering from neuropathic itch such as in PHI is a clinical challenge (as is the case for postherpetic pain)[1,4].

Etiologically, PHI follows a varicella zoster virus eruption but the mechanism(s) behind the development of chronic itch is currently unknown and in particular, it is unclear why patients develop highly diverse sensory symptomatology[15,16]. In this patient considerable sensory loss-of-function in the lesional skin area was evident for several QST parameters indicating defunctionalization of several cutaneous nerve fiber classes (**Fig. 1C**). In a previous case of severe postherpetic pruritus, hypoesthesia and hypoalgesia was also reported[7]. Using contralateral control QST data is generally associated with higher sensitivity than applying normative data for comparison and thus applied in this report[17]. However, it should be noted that while the recorded hypoesthesia to thermal and mechanical stimuli was pronounced also in comparison to a normative dataset, the heat hypoalgesia was to a large extent driven by low (but still within normal range)

HPT in the unaffected control area[17]. In the present study the hypoesthesia but not the hypoalgesia in the affected skin area gradually reversed during the 1 year that the patient was followed and this decline corresponded to the reduction of itch. The tested PHI patient appear to fit the "sensory-loss phenotype" frequently described in large QST studies in neuropathic pain patients. It is seemingly paradoxical that considerable multimodal loss of sensory function in a skin area can produce insatiable spontaneous and touch-evoked itch. A conceivable mechanism via which this could occur is a loss of afferent sensibility to tactile and thermal stimuli in the area caused by the varicella zoster eruption leading to spinal disinhibition of itch transmission from remaining pruriceptive fibers. A similar pathoetiology has previously been suggested and seems to be consistent with the fact that pruriception is highly gated at the spinal level by both nociceptive and mechanoreceptive input through recently discovered distinct populations of itch-specific inhibitory interneurons[4,18]. Another potential mechanism that could be involved is selective peripheral sensitization of pruriceptive nociceptors perhaps prompted secondarily to skin damage and inflammatory mediators associated with the virus eruption. However, this mechanism alone can hardly explain the chronicity of the itch and the sensory loss occurring in the area. Notably, HPT, which can be increased by capsaicin treatment, did not show signs of normalization during the repeated capsaicin treatments. This is unlikely to be related to the capsaicin treatments however, since previous studies have not shown any prolonged increase in HPT in healthy controls[19] or neuropathic pain patients following an 8% capsaicin treatment. Morever, WDT which is in fact profoundly increased by 8% capsaicin did normalize substantially in our patient[20]. Similarly, the slow but gradual normalization of thermal and mechanical detection thresholds is likely associated with natural recovery rather than the treatment since another study found no effect on MDT alongside prolonged warmth hypoesthesia following a single 8% capsaicin treatment[20].

Itch and pain are highly entwined sensory modalities and it has previously been described that while certain analgesics have a favorable effect on itch (eg, κ-opioid-agonists, lidocaine, and gabapentinoids) others may evoke and exacerbate itch (eg, μ-opioids)[21]. In the present case, 4 cycles of topical 8% capsaicin effectively alleviated chronic PHI and was well tolerated by the patient when tramadol was applied before the capsaicin treatments. Previous case studies of neuropathic itch have found a similar effect of 8% topical capsaicin and often noted significant improvements following a single treatment only.

As the spatial acuity of itch is poor, probing the area of touch-evoked itch manually or with a von Frey filament (as previously described[12] is a useful way to determine the exact area of patch application in patients without visible skin manifestations). A previous brief review describes practical aspects of conducting 8% capsaicin patch treatments for neuropathic itch conditions[22].

Further studies using both QSTs designed for general somatosensory assessment (eg, the DFNS methodology) as well as QST tailored specifically for chronic itch patients, for example, gain/loss of pruriceptive function, are needed. Although significant sensory loss have previously been noted in a patient with PHI it is unclear whether the presently observed aberrations are typical for neuropathic itch conditions as only case studies have been published. In conclusion, there seem to be no hindrances to applying 8% topical capsaicin with intractable PHI as an indication, but future RCTs are needed to adequately elucidate its efficacy and safety profile in this patient group.

Conflict of interest statement

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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