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Quantitative sensory testing in notalgia paresthetica reveals small fiber-type–specific differences in non-pruritic sensitivity: a pilot study

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Abstract

Introduction: Notalgia paresthetica (NP) is a chronic condition characterized by pruritus and other unpleasant dysesthetic sensations unilaterally on the subscapular back. Its specific underlying mechanisms are largely unknown, though hypothesized to be neuropathic. Determination of possible somatosensory contributors to the condition could pave the way for novel treatments.

Objectives: Given the potential involvement of non-pruritic mechanisms in NP, our objective was to broadly characterize the somatosensory function in NP-affected and unaffected skin using methods that have been standardized in pain-free controls and painful neuropathic disorders. We hypothesized that if NP is caused by neuropathic mechanisms not targeted directly to pruritoceptors in the skin, somatosensory abnormalities would not be itchspecific. Second, given the lack of symptoms on the contralateral side of the back, we hypothesized that this region would be normally sensitive.

Methods: In this study, quantitative sensory testing (QST) was used to comprehensively assess the somatosensory function in 15 adult patients with NP. Standardized QST metrics were performed in the NP-affected region and compared with the contralateral asymptomatic skin and itch-free individuals using an age, gender, and site-matched reference data set.

Results: There were no significant differences in sensitivity between symptomatic and asymptomatic skin, except for increased mechanical-evoked itch on the itchy side. However, reference data set comparisons revealed bilateral hyposensitivity to innocuous cold and noxious pinprick and higher temporal summation of pain in patients with NP. In addition, compared with reference data, patients with NP demonstrated decreased sensitivity to cold and pinprick, presence of paradoxical heat sensations, and increased wind-up of pain.

Conclusion: These results suggest a role for Aδ fiber pathways and central sensitization in NP-associated itch. More research is needed to determine whether sensory differences extend beyond the NP-affected dermatomal level and what might cause neuropathy specifically targeting Aδ fibers.

Keywords: Neuropathic, Pruritus, Dysesthesia, Sensation, Somatosensory disorders, Quantitative sensory testing

1. Introduction

Notalgia paresthetica (NP) is a chronic cutaneous dysesthesia characterized by pruritus and dysesthetic sensations unilaterally on the subscapular back. There is a complete absence of primary skin lesions, though secondary changes including hyperpigmentation, lichenification, and excoriations can occur due to scratching. Notalgia paresthetica is considered a subtype of neuropathic itch, possibly due to nerve entrapment and/or degenerative spinal changes, but a recent study found no association between spinal pathology and NP severity.[14] Skin biopsies have suggested both increased and decreased epidermal nerve fiber density in NP,[4,15] and no changes in cutaneous morphology have been observed that cannot be explained by chronic scratching. Of the therapies used for NP, including oral

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medications (gabapentin and amitriptyline), topicals, and intradermal therapies (lidocaine and botulinum toxin), topical capsaicin has the most evidence of effectiveness,[17] suggesting that the signals generating chronic itch in NP likely originate in the skin, even if the pathology is more proximal. This is supported by the newest therapeutic option on the market, difelikefalin (Korsuva, Cara Therapeutics), a selective kappa opioid receptor agonist that acts principally on peripheral sensory neurons and has performed well in clinical trials for NP.[5]

There are pruritic-specific pathways ("labeled lines" for itch) from the periphery to the brain, but there is also strong evidence of interactions with other sensory modalities.[13] For example, cutaneous application of cool temperatures or menthol, an agonist of the cold-responsive transient receptor potential melastatin 8 (TRPM8) channel, inhibits itch.[1] The dulling of itch sensations by skin cooling in NP is so well established that it is colloquially referred to as the "ice pack sign." The inhibition of itch by menthol, which activates cold fibers but does not physically cool the skin, suggests that this interaction likely occurs in second-order neurons in the spinal cord.

Given the potential involvement of non-pruritic mechanisms in NP, our objective was to broadly characterize the somatosensory function in NP-affected and unaffected skin using methods that have been standardized in pain-free controls and painful neuropathic disorders. We hypothesized that if NP is caused by neuropathic mechanisms not targeted directly to pruritoceptors in the skin, somatosensory abnormalities would not be itch-specific. Second, given the lack of symptoms on the contralateral side of the back, we hypothesized that this region would be normally sensitive.

2. Methods

Fifteen individuals with dermatologist-diagnosed NP and an itch score ≥1 on a scale from 0 (no itch) to 10 (worst itch) were recruited from a university-based dermatology clinic. Prospective subjects underwent examination by a board-certified dermatologist to confirm the diagnosis of NP and to exclude patients with concomitant confounding primary skin disorders. As there are no standard diagnostic criteria for NP, diagnosis was based on the presence of typical symptoms (localized pruritus located unilaterally on the subscapular back) in the absence of any primary skin disease. Secondary changes, such as lichenification or excoriation, may or may not have been present. Individuals with probable or diagnosed neuropathy, history of spinal injury, or any other clinically relevant sensory deficits were excluded.

The impact of NP on quality of life was assessed using the ItchyQoL questionnaire.[2] Cutaneous pain was assessed using the Short-Form McGill Pain Questionnaire (SF-MPQ).[9] Quantitative sensory testing (QST) was performed according to the German Research Network on Neuropathic Pain (DFNS) standardized protocol[12] in NP-affected skin and on a control site on the contralateral back at the same dermatomal level. The NP-affected testing site was selected as the area inferior to the medial border of the scapula subjectively rated as the itchiest by the patient. The control site was the same location (inferior to the medial border of the scapula) at the same dermatomal level on the contralateral back. Participants also rated the itchiness of dynamic mechanical stimuli to assess evoked itch sensations (alloknesis). Detailed methods are provided in the supplemental material, http://links.lww.com/PR9/A233.

Sensitivity was compared between NP-affected and control sites as well as to published age and gender-matched reference data from the trunk.[11] For NP symptomatic-to-asymptomatic skin comparisons, QST metrics were analyzed using paired-sample *t* tests with the exception of alloknesis; here, a Wilcoxon signed-rank test was used due to non-normality. When comparing patients with NP with reference data, significance was assessed using independent sample *t* tests (df = 28), following log and Z-score transformations of NP patient data as recommended by DFNS.[8,11] This method of z-score normalization has been recommended to permit comparisons with the DFNS reference data without the need to subsample subjects from the database.[8] The study was approved by the Emory University Institutional Review Board. Significance was set to $P < 0.05$, 2-tailed.

3. Results

The study sample of 15 patients was predominantly female (n = 12, 80%) and White (n = 9, 60%). Notalgia paresthetica occurred most commonly on the right side (n = 9, 60%). The mean duration of disease was 12.0 ± 10.3 years (range: 1–33 years). Itch severity was rated as "Mild" (n = 9) and "Moderate" (n = 6) based on ItchyQoL severity bands.[6] Additional patient characteristics are included in **Table 1**.

Notalgia paresthetica–affected skin regions demonstrated remarkably similar sensitivity to the contralateral asymptomatic skin ($P > 0.10$ for all), with the exception of evoked itch sensations (alloknesis), which were significantly elevated in symptomatic (M = 4.0, SD = 7.0) compared to asymptomatic (M = 0.8, SD = 1.7) skin ($Z = 2.67$, $P = 0.008$, see **Fig. 1)**. However, when compared with reference data, both NP-affected skin and contralateral asymptomatic skin had similarly decreased sensitivity to detect warm-to-cold-to-warm changes ($P = 0.04$ and $P = 0.02$), decreased pinprick pain sensitivity ($P = 0.01$ and $P = 0.003$), and increased pain wind-up with repeated pinpricks ($P = 0.01$ and $P = 0.02$, respectively, see **Fig. 2)**. In addition, both sites showed decreased cold sensitivity, although this only reached statistical significance on NP-affected skin ($P = 0.01$; asymptomatic skin $P = 0.07$). There were some cases of allodynia and paradoxical heat as are common in some types of neuropathic pain, but the more predominant paradoxical finding was that of alloknesis, which was present in 60% of patients in their symptomatic skin (**Table 2)**.

4. Discussion

A comprehensive QST assessment in patients with NP revealed similar sensitivity in affected and asymptomatic skin, with the exception of increased mechanical-evoked itch in symptomatic skin. Both sites demonstrated loss of cold and pinprick sensations, some cases of paradoxical sensations, and increased pain wind-up compared with itch-free controls.

Innocuous cold inhibits both pain and itch. Blocking cold fibers experimentally causes anesthesia for cold and paradoxical heat sensations (ie, cold feels burning hot).[16] Both loss of cold sensation and paradoxical heat sensations are commonly observed in certain types of neuropathic pain,[11] and the cases of paradoxical heat in NP support the idea that this type of itch is also neuropathic. The inhibition of itch by cold, the clinical observation that NP is alleviated by cold, and the diminished cold sensitivity in patients with NP in this study are all consistent with the hypothesis that NP involves an unmasking of itch signals by a deficit in the central itch-inhibitory effects of cold-transmission fibers. Interestingly, in our cohort, the third most common sensory descriptor on the Short-Form McGill Pain Questionnaire was "Hot," only behind "Sharp" and "Tender."

Table 1

Patient demographic and clinical characteristics.

	Study cohort (n = 15)	Reference data (n = 162)[11]
Age, y (mean ± SD)	64.0 ± 10.0	42.5 ± 14.8
Sex (#, %)		
Female	12 (80.0)	104 (64.2)
Male	3 (20.0)	58 (35.8)
Race/ethnicity (#, %)		
White	9 (60.0)	NR
Black	4 (26.6)	NR
Middle/Near Eastern	1 (6.7)	NR
Hispanic	1 (6.7)	NR
ItchyQoL severity (#, %)[2,6]		
Little (0–30)	0 (0)	NR
Mild (31–50)	9 (60.0)	NR
Moderate (51–80)	6 (40.0)	NR
Severe (81+)	0 (0)	NR
SF-McGill Pain Questionnaire (median, IQR)[9]		
Total	10.0 [6.0]	NR
Sensory	8.0 [5.5]	NR
Affective	1.0 [2.0]	NR

IQR, interquartile range; NR, not reported.

Cold and painful pinprick are both known to activate Aδ fibers.[7] In the spinal cord dorsal horn, there are populations of second-order spinothalamic tract neurons specific for innocuous cold and nociceptive information, suggesting that a deficit in one might not affect the other. However, Aδ and C fibers preferentially terminate in different locations in the dorsal horn.[3] While speculative, a spinal impingement that is somehow focused on Aδ-transmitting neuronal populations could explain a concomitant loss of cold and pinprick pain, or it could be a peripheral or localized effect on myelin, which C-fibers do not have.

In contrast to these sensory deficits, patients with NP displayed increased temporal summation of pain, a process that enhances C-fiber signal transmission to the brain. Temporal summation of itch, which is also C-fiber–mediated, has not been systematically demonstrated, but there is evidence that prolonged input onto second-order itch neurons is required for them to fire action potentials.[13] The overlap between pain and itch is considerable, including some nociceptors that can signal both itch and pain under different conditions.[13] Increased pain wind-up reflects an n-methyl D aspartate (NMDA) receptor–mediated central sensitization process that often occurs in chronic pain.[10] A definitive link of central sensitization to itch has yet to be established, but it is plausible that similar processes could enhance peripheral pruritoceptive drive onto second-order itch neurons. These QST results taken together may imply an impingement of Aδ and an enhancement of C-fiber activity, but more research is needed.

The QST reference data set also included a group of patients with a neuropathic pain condition affecting the mid-to-upper back unilaterally, postherpetic neuralgia (PHN).[11] This group also demonstrated decreased sensitivity to cold but, in addition, showed a loss of innocuous warmth and touch and higher rates of dynamic mechanical allodynia. While some patients with PHN had deficits in pinprick pain, others had enhancement, in contrast to the uniform loss of pinprick sensitivity in NP. Dynamic mechanical allodynia was found in 60% of patients with PHN[11] and was also apparent in some cases of NP in this study, but alloknesis was much more common in NP (60% of itchy sites). The ability to evoke itch sensations with peripheral stimulation and the ability to decrease spontaneous itch with topical and/or intradermal cold, menthol, capsaicin, and lidocaine suggests that peripheral pruritoceptive drive plays an important role in the chronic itchy sensations experienced by patients with NP.

This study has some limitations. The first and most serious limitation is the lack of internal healthy control data. However, the published reference data used for comparison are large and multi-institutional (collected at 10 centers across Germany), which are sufficiently robust for comparison with these pilot data. In addition, although the statistical method used to compare QST data with the DFNS reference set has been previously recommended for this type of analysis, it may be prone to false-positive results, particularly given the lack of internal healthy control subjects. Enrolling healthy control subjects in future studies will enhance statistical comparisons with the DFNS reference data. It is unclear whether sensory changes extend beyond the dermatomal level where NP is experienced, and future studies should perform QST at multiple segmental levels. There is a lack of published QST reference data in American subjects, and it is unclear whether differences in nationality may result in systematic variations in QST results. Finally, these results are consistent with the proposition that NP is a neuropathic itch condition that may involve a lack of cold inhibition,[1,16] but QST alone cannot provide definitive evidence of this. Future research should be performed

Table 2

Patient-reported abnormal sensory experiences.

Abnormal sensory experience		No. (%) reporting on ≥1 trials	
		Asymptomatic skin	Itchy skin
Thermal	Paradoxical heat sensations (PHS)	2 (13.3)*	4 (26.7)
Mechanical	Dynamic mechanical allodynia (DMA)	2 (13.3)	2 (13.3)
	Alloknesis	5 (33.3)	9 (60.0)

* One patient included here reported paradoxical cold (feeling cold upon skin warming), which is not technically PHS.

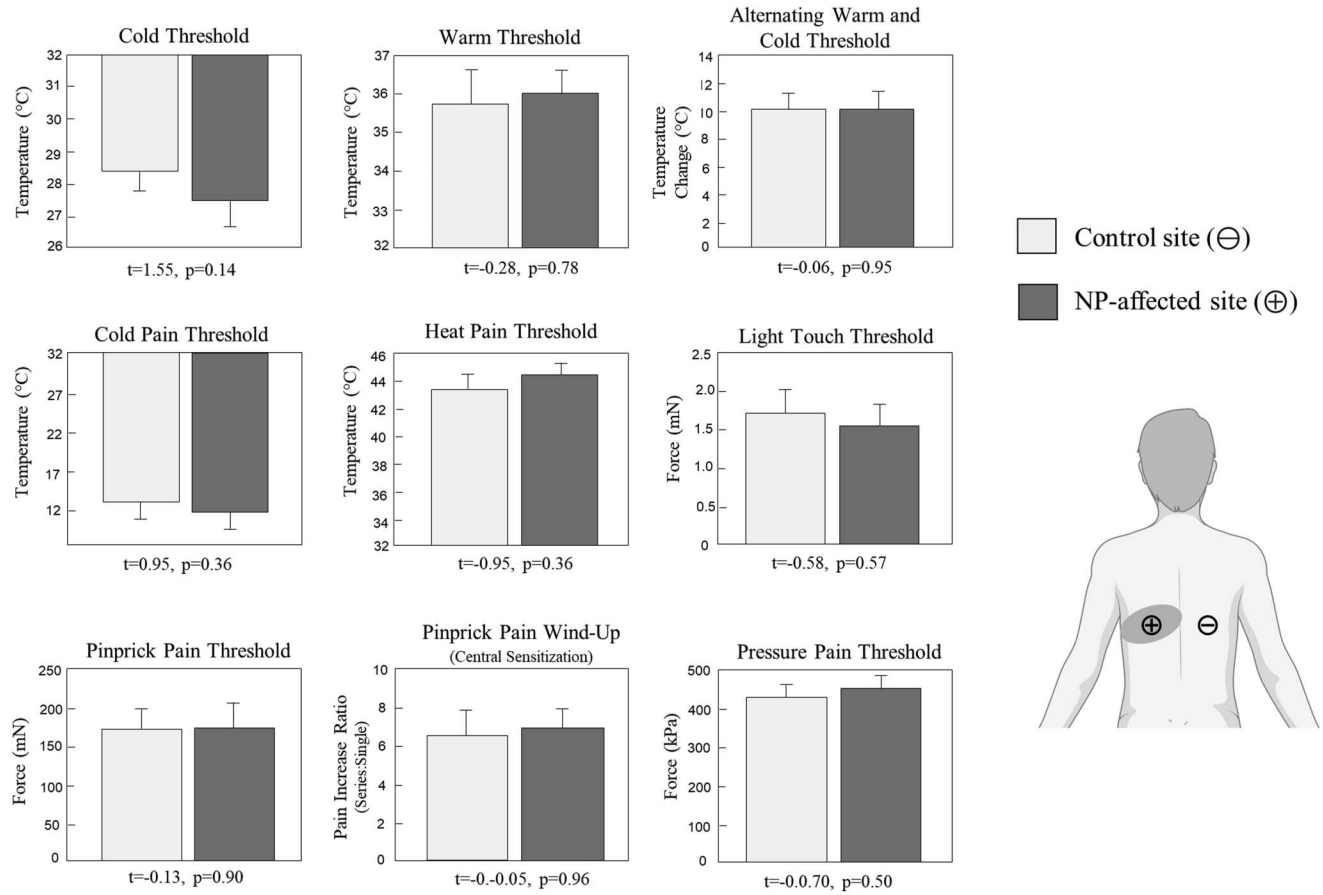

Figure 1. QST results from patients with notalgia paresthetica (NP) comparing NP-affected skin with unaffected skin on the contralateral back. Sensitivity to various types of innocuous and noxious stimulation was not different in itchy vs contralateral itch-free skin. The results of paired-sample *t* tests including the t value and *P* value (2-tailed) are depicted below each bar graph.

on a larger sample of patients with NP and internal healthy controls and include a combination of QST and physiological outcomes such as assessment of intraepidermal nerve fiber density.

In conclusion, NP is marked by a loss of cold and pinprick sensitivity and enhancement of pain wind-up in both itchy and contralateral, asymptomatic skin. While these data support the idea that there are central alterations in sensory processing (and likely neuropathy) in NP, they also highlight the role of peripheral pruritoceptors in the affected skin area in evoking itch sensations. Further studies are needed to elucidate the exact pathophysiology, which may lead to novel treatments of this condition.

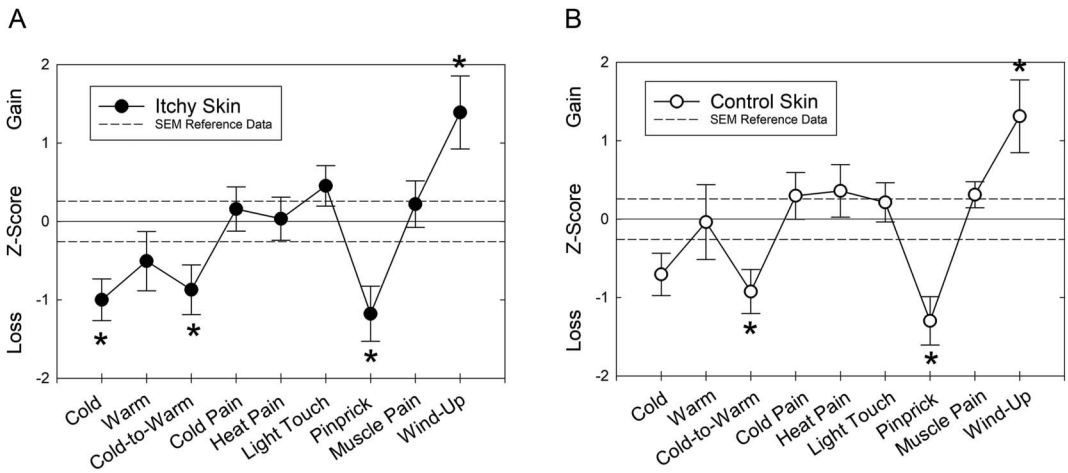

Figure 2. QST results in NP-affected skin (A) and contralateral unaffected skin (B) compared with age and gender-matched reference data from the trunk.[11] The horizontal line on the figures represents the mean value of the control data Z-score, which was always 0, and the dotted lines show the standard error of the mean. Values <0 indicate sensory losses and >0 sensory gains, compared with itch-free controls. *$P < 0.05$. NP, notalgia paresthetica; QST, quantitative sensory testing.

Disclosures

The authors have no conflict of interest to declare.

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