The relationship of pain, allodynia and thermal sensation in post-herpetic neuralgia

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Summary
In the syndrome of post-herpetic neuralgia (PHN), the nature of the sensory disturbance and its relationship both to the severity and cause of the pain is controversial. To address these issues, sensory mapping and quantitative thermal sensory testing was carried out four times in separate sessions on 35 subjects with established PHN. All subjects had pain affecting the torso or extremities and brush-evoked allodynia. Each session included rating of ongoing pain, mapping of the area of any sensory disturbance and the area of greatest pain, grading of allodynia severity within the area of greatest ongoing pain, and quantitative testing of thermal sensation in both the painful and the contralateral unaffected mirror-image skin. The severity of allodynia was positively correlated with reported ongoing pain severity. As a group, subjects had a sensory deficit to thermal stimuli in PHN skin compared with unaffected mirror-image skin. However, the magnitude of the heat pain sensory deficit was inversely correlated with both pain intensity and severity of allodynia. In fact, 12 subjects had heat hyperalgesia in their region of maximum pain. Compared with the 23 subjects with heat hypoalgesia, the group of 12 heat hyperalgesic subjects had significantly higher pain ratings and allodynia severity. Sensory loss was less strongly, but still inversely related to pain severity for the thermal modalities of innocuous warming, cooling and cold pain. This implies that there is no simple relationship between loss of peripheral nerve function and spontaneous or evoked pain. Rather, the preservation of several sensory modalities in their area of maximal pain suggests that in some PHN patients, activity in primary afferent nociceptors that remain connected to both their peripheral and central targets contributes significantly to ongoing pain. Although other mechanisms are likely to contribute to the pain, the demonstrated responsivity of PHN to topical agents including local anaesthetics, capsaicin, and non-steroidal anti-inflammatory drugs, supports this proposed mechanism of pain generation.

Keywords: neuropathic pain; varicella-zoster virus; hyperalgesia; quantitative sensory testing; primary afferent nociceptors

Abbreviations: PHN = post-herpetic neuralgia; VAS = visual analog scale

Introduction
Neurologists have long been fascinated by the apparent paradox that damage to sensory pathways, usually associated with loss of function, is occasionally accompanied by dramatic evidence of hyperfunction. Nowhere is this more evident than in the pain that sometimes accompanies peripheral nerve injury. A common example of this is PHN following acute herpes zoster, a disease that consistently affects dorsal root ganglion neurons. During recrudescence of the varicella-zoster virus, the infected dorsal root ganglion and its processes are attacked and may be severely damaged from the spinal cord to the epidermis. Because enduring sensory loss is common, it is natural to attribute continuing pain to loss of function.

Early clinical studies of patients with PHN demonstrated deficits in the perception of single gentle touches, pinprick, heat and cold which were greatest in the centre of the painful area and faded toward the boundary between involved and normal skin (Noordenbos, 1959). Based on these findings, Noordenbos proposed that the pain and sensory disturbances in PHN are due to the loss of the central inhibitory effect on pain produced by input from large diameter fibres that respond maximally to light mechanical stimulation. However, subsequent observers clearly documented deficits in pain and temperature sensation as well as in response to light mechanical stimulation (Watson et al., 1988; Nurmikko and Bowsher, 1990). Because PHN is frequently accompanied by loss of function of primary afferents of large and small diameter, investigators have emphasized deafferentation...
induced CNS reorganization as the major pain mechanism in PHN (Baron and Saguer, 1993; Bowsher, 1993; Watson and Deck, 1993; Nurmikko, 1994).

In contrast to this emphasis on deafferentation as the major cause of pain, recent studies on animals with experimental peripheral nerve injury have shown that some damaged primary afferents become spontaneously active and have lowered thresholds to physiological stimuli (Wall and Gutnick, 1974; Scadding, 1981; Tanelian and Maclver, 1991; Koltzenburg et al., 1994b). The primary afferents that show this change include A-delta and C-fibres, including primary afferent nociceptors. There is evidence that similar changes in primary afferent function occur in humans with nerve injury (Nystrom and Hagbarth, 1981; Cline et al., 1989; Koltzenburg et al., 1994a).

In a previous study of PHN patients (1989), we were struck by how many patients with severe pain had little, if any, sensory deficit in the region they felt was the source of their most severe pain. Furthermore, infrared thermography showed that these painfully sensitive skin regions were warm in some patients, a possible reflection of antidromic impulses causing release of vasoactive peptides from small diameter primary afferents. Local anaesthetic skin infiltration of the most painful area produced relief greater than could be explained by systemic absorption, leading us to propose that afferent activity arising from a source near the skin surface was a major factor in producing pain. This idea was supported by double-blind, vehicle controlled studies demonstrating that topical local anaesthetic application relieves PHN pain through a direct action on painfully sensitive skin (Rowbotham et al., 1995). Repetitive topical application of capsaicin, a selective C-fibre neurotoxin, has also been shown to relieve the pain of PHN in some patients (Bernstein et al., 1989; Bjerring et al., 1990; Watson et al., 1993).

In the present study we have used quantitative thermal sensory measurement to test the hypothesis that activity in primary afferent nociceptors, in continuity with both their peripheral and central targets, contributes significantly to the pain in some PHN patients. We also examined the hypothesis, that input from nociceptors-in-continuity contributes to central sensitization and allodynia to light moving mechanical stimuli, by examining the correlations among pain intensity, allodynia severity and thermal sensory thresholds.

Methods

Subjects and study sessions

Subjects with PHN, defined as pain present for >1 month after healing of the skin rash, a well-defined area of painfully sensitive skin on the torso or limbs, stable health, intact cognition and without previous neurolytic or neurosurgical therapy for PHN, were recruited for participation in the four session study through newspaper advertisements and newsletters to health care providers. Subjects participating in this study were simultaneously enrolled in a four session prospective clinical trial of topical local anaesthetic application that has been reported elsewhere (Rowbotham et al., 1996). In that double-blind, random order study, a local anaesthetic patch was applied during two 12-h sessions, a vehicle patch was applied during one 12-h session, and one session was a no-treatment control. Data analysis of that study indicated that over the 2–4 weeks for each subject, there was no carry-over effect from session to session on either pain severity or sensory testing results.

Any use of topical medications for PHN was discontinued at least 2 weeks prior to the first study session. During the study, subjects were instructed not to use any topically applied medications or salves on the area affected by PHN. Subjects were allowed to continue ‘as needed’ use of oral medications for control of PHN pain, including antidepressants and opioid analgesics, but were not allowed to start new oral medications during the study. A diary was kept by all subjects to record their medication use. All sessions were carried out at the UCSF Pain Clinical Research Center. Sessions were at least 72 h apart and were typically 1 week apart.

All subjects gave informed consent prior to participation, and the study was approved by the Committee on Human Research at the University of California, San Francisco.

Subject assessment

Pain intensity was assessed using a horizontal 100 mm visual analog scale (VAS). The subject indicated the severity of his or her PHN pain with a mark along the line between ‘no pain’ (0 mm) and ‘worst pain imaginable’ (100 mm). At each session, a VAS score was obtained before any other testing was initiated.

The mapping and sensory testing scheme is shown in Fig. 1. The full sequence of mapping and sensory testing was repeated at all four sessions. Two areas were mapped on the subject’s skin: (i) the borders of the area of any PHN related sensory abnormality (painful or non-painful) produced by gentle mechanical stimulation; (ii) the area of greatest PHN pain. Subjects first indicated on a pain drawing, and verbally described, the area of maximal PHN pain. The borders of the two areas of interest were confirmed on the subject’s skin, marked and then photographed. Skin markings were made after touching the patient’s skin to corroborate the location of the borders. Surface area affected was estimated visually from the photographs.

Sensory examination was carried out within the area of greatest pain and the contralateral unaffected mirror-image skin area. Allodynia to gently stroking the skin with a cotton swab was only tested within the area of maximal pain. Allodynia was graded as absent (0), mildly painful (1+), moderately painful (2+) or severely painful (3+). Quantitative thermal sensory testing was carried out using the Somedic Thermotest (Somedic AB, Stockholm). The 12 cm² surface area thermode is a Peltier device that warms the skin surface at a linear rate to a cut-off of 51°C and cools it...
For allodynia, the ratings for the four sessions were averaged to provide an overall pain intensity rating for that subject. For alldynia, the ratings for the four sessions for each subject were averaged. For each thermal modality, the median value of the three sites tested on each side of the body at each session was selected to represent the central tendency for that area instead of the mean because it is less sensitive to the machine safety cut-off values for outliers. For each subject, the median values for each session were then averaged to represent the overall value for the 12 separate ratings per thermal modality tested on each side of the body. Median values for the normal side were then compared with median values for the PHN side to calculate the sensory deficit for each thermal modality in degrees centigrade. Hypoaesthesia and hypoalgesia are represented by positive values. If a subject was hyperaesthetic to warmth or cooling, or hyperalgesic to heat or cold stimuli, the sensory deficit was a negative number.

Results

Subjects, pain area and pain ratings, and sensory testing data

Thirty-five subjects completed the study. There were 20 males and 15 females. The age range was 52–90 years, the mean age being 75 years. The duration of PHN ranged from 4 to 318 months, averaging 48 months. No subject had used capsaicin within 2 months of study entry. Thirteen subjects were using opioids and six subjects were taking antidepressants at the time of study entry.

Seven subjects had PHN in cervical dermatomes, 27 subjects had thoracic PHN and one subject had lumbar PHN. The range of visually estimated size of the most painful area was 80–750 cm², with a mean of 255 cm². The size of the area of any sensory abnormality related to PHN ranged from 224 to 2125 cm² with a mean of 737 cm². Although some patients had more than one discrete area of maximal pain, areas of maximal pain were always contained within an area of sensory abnormality.

The mean of the average pain VAS ratings for the four sessions was 48 mm (±16) on the 100 mm scale. There was no change in pain VAS for the group over the course of the four sessions. The mean of the average alldynia severity ratings for the subjects was 2.0 (±0.65) on the 0 to 3+ scale, without any change in severity for the group as a whole over the course of the study.

The group means (±1 SD) for the average median thermal thresholds for each side and each thermal modality are shown in Fig. 2. Comparing the painful side with the mirror-image unaffected side by paired t test for the entire group, the side affected by PHN had a sensory deficit compared with the contralateral unaffected area for all thermal modalities. For warm threshold, the mean deficit was 3.1°C (paired t test, \( P < 0.0001 \); range −1.6 to +12.0°C). For heat pain, the mean deficit was 1.9°C (\( P = 0.0004 \); range −3.0 to +7.6°C). For detecting cooling, the mean deficit was 3.3°C (\( P < 0.0001 \); range −0.7 to +12.5°C). For cold pain, the mean deficit was 2.7°C (\( P = 0.006 \); range −10.6 to +12.1°C). A box plot of the sensory deficit for each thermal modality is shown in Fig. 3.
Fig. 2 Thermal thresholds (°C) for PHN skin and contralateral, mirror-image unaffected skin. For each subject, the thermal threshold for each modality represents the average of the median value from each of the four sessions. Error bars are 1 SD. *P < 0.01; **P < 0.001; ***P < 0.0001

Fig. 3 Box plot of thermal sensory deficits. For each subject, the deficit calculation is based on the difference in the average median threshold between mirror-image unaffected skin and the most painful post-herpetic skin area for the four sessions. Positive values indicate a sensory deficit in post-herpetic skin, either hypoesthesia or hypoalgesia. Negative values indicate hyperesthesia/hyperalgesia in post-herpetic skin. The middle line in the box represents the median value for the subjects; the borders represent the 25th and 75th percentiles; the bars represent the 10th and 90th percentiles; and outliers are shown as circles.

Regression plot analysis showed no relationship between gender, age or duration of pain with pain VAS scores, allodynia severity or thermal thresholds. The size of the painful area was not correlated with pain severity or the magnitude of the thermal sensory deficit, but had a marginally significant positive correlation with allodynia severity (Kendall tau = 0.27, P = 0.02).

Relationships of pain intensity, allodynia severity and thermal sensory deficit
There was a significant positive correlation between the intensity of overall PHN pain as measured by 100 mm VAS and the severity of allodynia (Kendall tau = 0.48, P < 0.0001), as shown in Fig. 4.

The magnitude of the heat pain deficit in PHN skin was significantly and inversely correlated with pain intensity (r² = 0.24, P = 0.003), as shown in Fig. 5. Twelve of the 35 subjects were hyperalgesic to heat in PHN skin. Compared with the 23 subjects who were hypoalgesic to heat, the hyperalgesic subjects had significantly higher baseline pain intensity. The average VAS for heat hyperalgesic subjects was 62 mm and for heat hypoalgesic subjects, 41 mm (two-tailed unpaired t test, P = 0.0003). The average allodynia rating for the 12 heat hyperalgesic subjects was 2.4 and for the 23 heat hypoalgesic subjects 1.7 (Mann–Whitney U test, P = 0.002).

Within subjects, deficits in one thermal modality were correlated with deficits in other thermal modalities. Significant correlations were observed between heat pain threshold and warm threshold (r² = 0.28, P = 0.001), and between cold pain threshold and heat pain threshold (r² = 0.19, P = 0.008).
Importantly, comparing the 12 heat hyperalgesic subjects with the 23 heat pain hypoalgesic subjects showed significantly smaller sensory deficits in warm threshold (0.7°C versus 3.7°C, unpaired \(t\) test \(P = 0.001\)), cool threshold (1.9°C versus 4.1°C, \(P = 0.05\)), and cold pain threshold (−0.2°C versus 4.2°C, \(P = 0.02\)).

**Discussion**

The presence of sensory deficits has led to the idea that the pain of PHN is due to deafferentation and CNS reorganization (Baron and Saguer, 1993; Bowsher, 1993; Watson and Deck, 1993; Nurmikko, 1994). However, partial injury to peripheral nerve often leads to sensitization and spontaneous activity in primary afferents, including nociceptors, whose peripheral and central axonal processes remain in continuity with their usual targets (Koltzenburg et al., 1994b). In this case, just as with noxious stimulation without nerve injury, the pain results at least in part from activity in primary afferent nociceptors. In the present work we have studied the region of maximal pain severity in PHN patients with prominent allodynia. In this area, pain severity correlates with preservation, not loss, of thermal sensory function. This suggests that, rather than being due to deafferentation and central reorganization, a significant component of the pain in allodynic PHN is generated by activity in preserved primary afferent nociceptors.

This idea is contrary to the position articulated by Bowsher (1993), who emphasized the importance of deafferentation in the aetiology of PHN. His conclusions were supported by two studies. In the first, Nurmikko and Bowsher (1990) did sensory testing on 42 patients presenting for treatment of PHN. The group means for all sensory modalities tested (warm, cold and heat pain thresholds; tactile, pinprick, two-point discrimination and vibration thresholds) were abnormal compared with the unaffected mirror-image area. Allodynia to gently brushing the skin was present in 87% of their sample of PHN patients. Sensory deficits in two or more modalities in the area of PHN were present in 93% of the PHN patients. They also studied a group of 20 patients who had been diagnosed with herpes zoster by other physicians during the acute phase but had no pain when contacted for sensory testing at least 3 months after the acute attack. Examination of the area of the herpetic outbreak in those patients who did not have PHN revealed multi-modality sensory deficits in only 10% of the cases. Because patients free of PHN after zoster had largely normal sensation compared with PHN patients, they concluded that the development of PHN is associated with sensory deficit and that deafferentation is the cause of pain. In a second study, Nurmikko et al. (1990) examined the relationship of sensory deficits during acute zoster to the subsequent persistence of pain. Three months after the initial zoster infection, only seven out of 31 patients still complained of pain. As a group, patients in whom pain was persistent had greater elevations of non-noxious warm and cold detection thresholds during acute zoster. These data were taken as evidence supporting the crucial contribution of deafferentation to PHN pain.

The data in our study are in basic agreement with Nurmikko and Bowsher (1990), in that we also found that PHN patients as a group have a sensory deficit in the painful area. However, our interpretation is different. We interpret our finding that pain severity correlates inversely with thermal sensory deficit to indicate that damaged but surviving and relatively intact primary afferents contribute directly to pain. We view the presence of sensory deficits in this group of PHN patients mainly as an indication that injury to primary afferents has occurred rather than as a clue to the mechanism of pain. The presence of a sensory deficit is not surprising in view of the fact that varicella-zoster virus nucleic acid is present in dorsal root ganglion cells and, when reactivated, the virus attacks primary afferent neurons. It is our view that input from these altered primary afferent neurons, particularly nociceptors which have maintained continuity with their central and peripheral targets, contributes significantly to the pain of PHN. Another possibility is that undamaged primary afferent nociceptors which innervate the same region of skin and have become sensitized, contribute to the pain. The fact that peripheral local anaesthetic block of the innervation of affected skin provides dramatic (though temporary) pain relief is consistent with either possibility (Colding, 1973; Dan, 1985; Rowbotham and Fields, 1989; Nurmikko et al., 1991). Systemic local anaesthetics, which have been shown to block ectopically generated impulses in injured primary afferents (Chabal et al., 1989; Tanelian and MacIver, 1991; Devor et al., 1992), also reduce the pain of PHN (Shanbrom, 1961; Rowbotham et al., 1991).

Baron and Saguer (1993) have also published data in apparent conflict with the hypothesis that activity in primary afferent nociceptors is a direct cause of PHN pain. They studied primary afferent function in 10 patients with PHN and allodynia on examination, in three patients who did not experience PHN after zoster and in 10 healthy controls. Skin temperature, resistance and thermally evoked blood flow were the same in PHN skin and contralateral unininvolved skin. However, the flare reaction to iontophoresed histamine, which results from release of vasoactive neuropeptides primarily from unmyelinated cutaneous primary afferents, was significantly impaired in allodynic PHN skin. Because the severity of the defect in flare response was positively correlated with the severity of spontaneous pain complaint, they concluded that intact primary afferent nociceptors were not involved in the signalling and maintenance of allodynia. The major difference between their approach and the current study is their lack of quantitative psychophysical data on sensory function. Specifically, to assess sensory function they used only one stimulus, histamine iontophoresis, to evoke itch and pain and the responses were described only qualitatively. Thus their statement that the affected PHN skin had a deficit in chemically evoked pain should be considered as tentative. Furthermore, although iontophoresis of histamine does stimulate some unmyelinated primary afferent...
nociceptors and does evoke an axon flare response, it is clear that histamine activates only a subset of C-fibres and is more likely to produce itch than pain. Thus, Handwerker et al. (1991) studied the discharge patterns of human C-fibres induced by iontophoretic histamine, which produced itch, and topical mustard oil which produced burning pain. Mustard oil activated all histamine responsive units and excited additional histamine unresponsive units.

In favour of the idea that denervation is prominent in painful post-herpetic skin is the report that such skin is less sensitive to agents that directly stimulate cutaneous C-fibres, such as local mustard oil and capsaicin (Jansco et al., 1983; LeVasseur et al., 1990). However, in all studies of topical capsaicin therapy for PHN, burning pain with application has been reported in a significant percentage of patients. In the large double-blind study of 0.075% capsaicin, reported by Watson et al. (1993), 60% of the 74 capsaicin treated subjects reported burning. Capsaicin-induced burning was severe enough to cause 13 subjects to drop out of the study. Since capsaicin has been shown to be a relatively selective activator of unmyelinated primary afferent nociceptors, this is strong evidence that functioning nociceptors are present in the area of PHN pain. Multiple independent studies have shown that topically applied local anaesthetics, capsaicin and non-steroidal anti-inflammatory drugs relieve the pain of PHN (Stow et al., 1989; De Benedittis et al., 1992; King, 1993; Rowbotham et al., 1995). That their common mechanism of action is likely to be suppression of spontaneous activity in small diameter cutaneous primary afferents further supports nociceptor activity rather than deafferentation with central reorganization as the primary mechanism for the pain. Of particular relevance is the study of Bjerring et al. (1990) who used quantitative thermal sensory testing to investigate the change in sensory function following capsaicin treatment of PHN patients. In a group of eight patients who obtained a mean pain reduction of 24% within 1 week of daily treatment, they documented that capsaicin increased warm and heat pain threshold during the same time period. With further treatment, there was no additional sensory deficit or pain relief. This is consistent with a contribution to PHN pain by unmyelinated primary afferent nociceptors.

In the present study, 12 out of 35 subjects had heat hyperalgesia. This hyperalgesia may not reflect activity in a large population of preserved thermal nociceptors. Rather, it could reflect activity in a small residual number of nociceptors that are sensitized or that project to a sensitized population of CNS neurons. However, compared with the other subjects, those with heat hyperalgesia had significantly smaller deficits in other thermal modalities. Since primary afferents signalling innocuous cutaneous cooling and warming represent separate populations of small diameter fibres (Yarnitsky and Ochoa, 1990, 1991; Verdugo and Ochoa, 1992; Dyck et al., 1993) the preservation of these sensory functions further argues against the idea that the hyperalgesia occurs despite a markedly reduced population of small diameter primary afferents.

Activity in primary afferent nociceptors could contribute to the allodynia observed in this group of subjects with PHN. The more functioning primary afferent nociceptors that remain in the area of PHN pain, the greater the potential for generating a barrage of nociceptor activity conducted into the CNS. In fact, we found heat hyperalgesia and relative preservation of thermal sensory function to predict more severe pain and allodynia. As has been demonstrated in animals and man using acute injections of capsaicin, a pure nociceptor barrage can induce a state of sensitization of CNS pain transmission neurons (Simone et al., 1989, 1991; LaMotte, 1992; Koltzenburg, 1994a; Willis, 1994). Once the CNS is sensitized, activation of large diameter primary afferents by gentle mechanical stimulation shifts from being non-painful to painful and is demonstrable as an area of secondary hyperalgesia and allodynia. Normally, this state of central sensitization is transient; however, it appears that once established, only a low level of continuing C-nociceptor input is needed to maintain the secondary hyperalgesia. The correlation of allodynia severity with preservation of thermal nociceptive sensory function in the present study suggests that a similar mechanism may contribute to the allodynia of PHN.

It is important to point out that the subjects in the current study were chosen because they had significant allodynia. Although this is characteristic of most patients with PHN (Watson et al., 1988; Nurmikko and Bowsher, 1990) not all PHN patients have prominent allodynia. There are PHN patients who have profound sensory loss, minimal to no allodynia and who obtain no relief from infiltrating the painful area with local anaesthetic (Rowbotham and Fields, 1989). Such patients could be classified as having a form of PHN that is characterized by deafferentation. The mechanism of pain in this group remains obscure, but it is presumably related to the type of deafferentation and central reorganization alluded to by other investigators (Baron and Sägner, 1993; Nurmikko, 1994). It is also possible that, in some of these patients, the primary afferents are intact centrally but that their peripheral terminals are not in continuity with their normal cutaneous targets and are thus not activated by superficial stimuli. These issues warrant further study. Whatever the mechanism of pain is in these patients, it is apparently unrelated to firing in primary afferent nociceptors that remain in continuity with the painful skin area. Thus, it is likely that its pathophysiology is different to that supported by the current data and that there are at least two important mechanisms that contribute to the pain in PHN (Rowbotham and Fields, 1989; Fields and Rowbotham, 1994). It is likely that, in many PHN patients, both mechanisms contribute to different degrees. This may explain why many patients with this condition respond incompletely to topical therapies and some fail to respond even transiently to epidural nerve blocks.

In summary, the present study demonstrates that in patients
whose long-standing PHN includes a component of mechanical allodynia, thermal sensation is often relatively preserved within the area of greatest pain. Although de-afferentation with central reorganization may contribute to the pain in some PHN patients, the strong positive correlations of allodynia severity, ongoing pain and preservation of thermal sensory function favours the hypothesis that activity in small diameter primary afferents, including nociceptors, is a major factor maintaining PHN pain.

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