Heterogenous Patterns of Sensory Dysfunction in Postherpetic Neuralgia Suggest Multiple Pathophysiologic Mechanisms

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Background: Postherpetic neuralgia (PHN) is considered by some investigators to be predominantly a deafferentation-type central pain syndrome; others suggest that activity of remaining peripheral nociceptors plays a critical role. The authors investigated the sensory dysfunction in subjects with PHN of varying duration and at different sites to gain further insight into the mechanisms responsible for the clinical features of neuropathic pain. In addition, the relationships between ongoing pain and pain evoked by mechanical and thermal stimuli were compared in patients with trigeminal and truncal PHN, to determine if the pathophysiologic mechanisms differed among subjects.

Methods: In 63 subjects with PHN, quantitative sensory testing was performed in the region of maximum allodynia or ongoing pain and the corresponding contralateral site. The intensity of ongoing pain was recorded. Sensory thresholds for warmth, coolness, heat pain, and cold pain were determined. Pain induced by various mechanical stimuli (dynamic, static, punctate) was rated using a numerical rating scale of 0–10.

Results: The mean rating of ongoing PHN pain was 7.3 ± 2.0 (mean ± SD). Allodynia induced by one or more mechanical stimuli was observed in 78% of subjects. A smaller subset (40%) had hyperalgesia to heat or cold stimuli. In subjects with duration of PHN of ≤ 1 yr duration, but not in those with duration of > 1 yr, the intensity of ongoing pain correlated with intensity of allodynia induced by dynamic stimuli. Deficits in thresholds for heat and cold pain were observed in the affected region of subjects with PHN in the thoracic dermatomes (P < 0.005), but not in the trigeminal distribution. No relationship was observed between the thermal deficits and ongoing pain or mechanical allodynia in the groups of subjects with either trigeminal or thoracic PHN.

Conclusion: Despite a common cause, the patterns of sensory abnormalities differ between subjects. Particular differences were noted between groups with facial or truncal PHN and between groups with recent or more chronic PHN. The observations suggest that the relative contributions of peripheral and central mechanisms to the pathophysiology of pain differ among subjects and may vary over the course of PHN. (Key words: Allodynia; central sensitization; herpes zoster; hyperalgesia; neuropathic pain; shingles pain; varicella zoster.)

POSTHERPETIC neuralgia (PHN), a condition of debilitating neuropathic pain, is a common sequela to herpes zoster (shingles) in elderly patients. The duration of PHN is < 1 yr in 78% of patients with PHN but may persist for years or indefinitely in others. Reactivation of the varicella zoster virus causes variable extent of degeneration of primary afferent sensory neurons. PHN is characterized by ongoing pain and varying degrees of sensory deficits, allodynia, and hyperalgesia. It is a prototypical pain state that has been used as a model to study the pathophysiology of neuropathic pain and to develop new treatment strategies.

Quantitative sensory testing is a psychophysical approach used to characterize the sensory dysfunction in subjects with experimental or clinical pain. The characterization of sensory abnormalities using quantitative sensory testing may lead to a better understanding of the mechanisms of pain signaling and provide insights for rational therapeutic strategies.
Based on comparisons of sensory changes in patients with and without PHN after acute herpes zoster, Nurmiikko and Bowsher concluded that PHN was primarily a deafferentation pain syndrome resulting from plastic changes in the central nervous system. Rowbotham and Fields have recently hypothesized that activity in the intact nociceptors innervating the affected PHN sites plays an important role in the mechanisms of PHN. Hence, the relative importance of the central and peripheral mechanisms in PHN remains controversial.

We conducted quantitative sensory tests in a large population of patients with PHN not using analgesics to further characterize the variable sensory patterns. The relationships between ongoing and stimulus-evoked pain intensities and between magnitude of ongoing pain and cutaneous sensory deficits were investigated. We compared sensory abnormalities in patients with facial and truncal PHN to determine if their sensory abnormalities were similar. Because PHN often resolves within 1 yr, we examined the relationship between ongoing and stimulus-evoked pain in patients with PHN of < 1 yr in duration and those with PHN of longer duration. In addition, we assessed the effects of confounding variables such as age, gender, and the presence or absence of diabetic neuropathy on the severity of ongoing pain and allodynia.

Materials and Methods

Sixty-three adults with pain for longer than 3 months after the resolution of the cutaneous lesions of herpes zoster were enrolled. For most subjects, sensory testing was performed during the screening and evaluation period for a controlled clinical trial comparing the effects of tricyclic antidepressants and opioid analgesics on pain, function, and cognition. All subjects had their pain therapies, including any topical agents, discontinued for at least 2 weeks before quantitative sensory testing. None of the patients used topical capsaicin for at least 1 month before the sensory tests. Criteria for exclusion included dementia or encephalopathy, and an average intensity of ongoing PHN pain of 3 or less during the past 24 h on the numerical rating scale of 0–10 (on which 0 = no pain, 10 = the most intense pain imaginable). All subjects gave informed consent to participate in this study, which was approved by the institutional review board.

Mechanical and thermal sensory tests were performed in areas of intense allodynia within the PHN site and at the corresponding contralateral site. In subjects without allodynia, sensory testing was performed in the region of maximum pain as indicated by the patient. The region of dynamic allodynia was mapped by stroking the affected skin with a cotton swab from a site well outside the symptomatic region toward the painful region in at least four different directions. This region was tested with an 11- or 33-mN von Frey filament to define areas of intense allodynia to punctate stimuli. Two areas on the trunk or the extremities in which the patients were markedly allodynic were identified for subsequent thermal testing. A single site, the most allodynic spot, was chosen for testing on the face, because of space limitation. Ongoing pain and stimulus-evoked pain were rated by the subjects on the numerical rating scale of 0–10. Baseline ongoing pain ratings were obtained before the sensory testing. Pain induced by the different mechanical stimuli was rated independent of ongoing pain. The mechanical stimuli used were camel’s hair brush strokes (dynamic stimulus); a thermally neutral, 220-g brass probe applied for 3 s (static stimulus); and an ascending series of von Frey filaments of 11, 33, and 199 mN (puncture stimuli). Pain induced by pinprick, a mildly noxious stimulus, was also assessed in all except the first 12 patients. All stimuli were applied to the same spot in the skin once. All sensory tests were conducted by trained research coordinators to ensure that a standardized protocol was used. Subjects were asked to report their sensations as undetected, detected and nonpainful, or detected and painful. If the sensation was painful, the subjects were asked to rate the intensity of the stimulus-induced pain on the 0–10 numerical rating scale.

Quantitative thermal sensory tests were performed within the zone of dynamic allodynia using a Peltier device with a 2 x 2-cm probe (TSA 2001 Thermal Sensory Analyzer, Medoc, Compass Medical Technologies, Minneapolis, MN) and a modified Marstock technique. The probe of the Peltier device was centered at the sites of maximal punctate allodynia, as described previously. In the subset of patients without mechanical allodynia, thermal sensory tests were performed in the region of maximal pain. Sensory thresholds for warmth, coolness, heat pain, and cold pain were determined three times each in sequential order. The median of the responses to the application of three consecutive stimuli was defined as the threshold. If more than one site was tested on one side of the body, the median of all the threshold values was used as the threshold temperature. Starting from a baseline temperature of 30°C, stimuli were delivered with a ramp rate of 1°C/s. The lowest
stimulus temperature was 0°C and the highest 53°C. Subjects were instructed to press a button immediately upon perceiving the appropriate sensation. There was a 20-s interval between each threshold measurement during which the probe returned to the baseline temperature of 30°C.

Data Analysis
Evoked pain scores and thermal thresholds in the PHN-affected and contralateral unaffected sites were compared by nonparametric statistics using the Wilcoxon matched-pairs signed-rank test. The Spearman rank correlation was used for all correlation analyses. Data for the verbal pain scores obtained during tests with mechanical stimuli are presented as medians and percentiles. The thermal thresholds are presented as means ± SD. Hypoesthesia (increase in detection threshold for warmth; affected–unaffected threshold temperature) and a lower detection threshold for cool sensation (unaffected–affected threshold temperature) and hypoalgesia (similar changes in pain threshold for heat and cold stimuli) are presented as positive values. Hyperesthesia and hyperalgesia are presented as negative values. P < 0.05 was considered to be statistically significant. SPSS release 6.1 (SPSS Inc., Chicago, IL) was used to analyze the data.

Results
The demographic characteristics of the 63 subjects in the study are shown in table 1. Subjects had moderate to severe ongoing pain, with a mean pain rating of 7.3 on the 0–10 numerical pain scale. There was no gender-related difference in the ratings of ongoing pain (M:F 7.3 ± 1.8:7.3 ± 2.2; n = 28:35) or for pain evoked by the mechanical or thermal stimuli.

Pain Evoked by Mechanical Stimuli
Thirty-eight subjects had allodynia induced by the dynamic stimulus, 33 subjects reported pain after the static stimulus, and 23 subjects reported pain after the 11-mN punctate stimulus (fig. 1). In 28 subjects (44%), dynamic mechanical stimulation with the brush was the most painful stimulus, whereas in 23 subjects (37%) both the dynamic and static (brass-rod) stimuli induced similar pain. The magnitude of pain evoked by the different mechanical stimuli is presented in figure 2.

Seventy-eight percent (n = 49) of the subjects had pain induced by one or more of the three innocuous mechanical stimuli: brush, brass probe, or 11-mN von Frey hair (fig. 2). These mechanical stimuli were consistently non-painful in the unaffected side. Compared to the contralateral unaffected site, pain induced by punctate (33 and 199 mN von Frey’s; Z = 5.44 and 4.87, respectively; P < 0.001) or pinprick (Z = 4.28, P < 0.001) stimuli was significantly greater at the PHN affected side. There was a positive correlation between the pain evoked by the dynamic stimulus and the pain evoked by the static (R = 0.65, P < 0.001), punctate (R = 0.78, P < 0.001), and pinprick (R = 0.67, P < 0.001) stimuli.

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If the subjects with dynamic allodynia (n = 38) were stratified based on the duration of PHN, a significant correlation between ongoing pain and intensity of brush-evoked allodynia was found in subjects with PHN of 1 yr or less in duration ($R = 0.69; P = 0.003, n = 16$), but not in those with PHN of a duration of more than 1 yr ($R = -0.05, P = 0.82, n = 22$; fig. 3). A similar trend was observed in comparing the correlation between ongoing pain and pressure-evoked pain in subjects with static allodynia (n = 33) with PHN for ≤ 1 yr ($R = 0.51$) versus > 1 yr ($R = -0.09; P = 0.1$ vs. 0.68, n = 11 and 22, respectively). There was also a closer correlation between ongoing pain and pain on pinprick in patients with PHN for ≤ 1 yr ($R = 0.54, P = 0.07, n = 12$) than in patients with PHN for > 1 yr ($R = 0.09, P = 0.77, n = 12$).

No correlation was found between the age of the subjects and the intensity of ongoing PHN pain or the intensity of allodynia to any of the mechanical stimuli. Ten percent of the subjects (n = 6) with PHN had diabetes mellitus and clinical evidence of a sensory neuropathy. In comparison with the nondiabetic subjects, the diabetic patients did not show a significant difference in either the severity of mechanical allodynia or the intensity of ongoing pain.

**Thermal Sensory Tests**

Three subjects did not report pain from the 53°C heat stimulus at both the unaffected and the affected sides. Similarly, eight subjects did not report pain from 0°C stimuli to both the affected and contralateral sides. Sig-
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Fig. 4. Mean thermal detection thresholds in the PHN-affected and mirror-image unaffected sites. As a group, the subjects demonstrated hypoaesthesia to warmth and cool sensation, and hypoalgesia to heat pain and cold pain. Thermal sensory tests were conducted in the same locations as the mechanical testing. Sensory thresholds for warmth, coolness, heat pain, and cold pain sensations were determined three times each. The median of the responses to the application of the consecutive stimuli was considered as the threshold at a given site. The base temperature (30°C) changed at a ramp rate of 1°C/s (cutoff temperatures = 0°C and 53°C). Data are mean ± SEM. Numbers indicate number of subjects tested for each modality. Data from all subjects are included for calculation of group means, except those whose heat and cold thresholds in the unaffected, mirror-image skin were > 53°C or < 0°C, respectively.

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SIGNIFICANT DEFICITS IN THE DETECTION OF THERMAL STIMULI (HYPOAESTHESIA) AND PAIN INDUCED BY HEAT OR COLD STIMULI (HYPOALGESIA) WERE FOUND AT THE PHN-AFFECTED SITES IF THE THRESHOLDS FOR EACH SUBJECT WERE COMPARED WITH THOSE FROM THE CONTRALATERAL UNAFFECTED SITES (THERMAL THRESHOLD: 42.5 ± 5.9 VS. 38.4 ± 4.9, AFFECTED VS. UNAFFECTED, RESPECTIVELY, [Z = 4.44, P < 0.001, N = 62]; COOLNESS THRESHOLD: 18.8 ± 9.3 VS. 24.9 ± 5.0 [Z = 5.58, P < 0.001, N = 62]; HEAT PAIN THRESHOLD: 46.6 ± 5.2 VS. 44.5 ± 5.4 [Z = 2.35, P = 0.02, N = 60]; COLD PAIN THRESHOLD: 9.2 ± 9.7 VS. 14.2 ± 8.9 [Z = 3.51, P = 0.004, N = 54]) (FIG. 4).

Although the mean thermal thresholds were elevated in the subjects as a whole, a subset (n = 25; 40%) had hyperalgesia to heat or cold stimuli, as defined by a greater than 1°C difference in mean threshold between the affected and unaffected sides. Eighteen subjects had a > 1°C decrease in heat pain threshold, and 13 subjects had a > 1°C decrease in cold pain threshold. Six subjects had decreased thresholds for both heat and cold pain (heat and cold hyperalgesia). As a more conservative measure, the variances from the mean for the multiple heat and cold pain threshold measurements in the unaffected side were calculated for each subject, and the SD of the mean variance in the population was determined. If this more conservative measure of a difference in thermal pain thresholds was used (affected side differing from the unaffected side by > 1 SD of the mean variance in the unaffected side), 13 subjects had heat hyperalgesia and 9 subjects had cold hyperalgesia.

In subjects with hyperalgesia to heat stimuli, the relationships between heat hyperalgesia and deficits in thermal thresholds were examined. There were no significant relationships within the whole group. If subjects were dichotomized based on the duration of PHN, there was a trend toward a correlation between heat pain deficits and intensity of ongoing pain in subjects with PHN of duration of ≤ 1 yr (R = 0.64, P = 0.06, n = 9), but not in those with PHN of longer duration (R = −0.12, P = 0.75, n = 10).

**Relationship of Pain to Sensory Deficits**

There were no significant correlations between the intensity of ongoing PHN pain and the differences in thermal thresholds between the affected and unaffected sides for warmth, coolness, heat pain, and cold pain (fig. 5). Similarly, no correlation was observed between the differences in thermal thresholds and the magnitude of allodynia induced by mechanical stimuli. However, the deficits in heat pain and cold pain thresholds in the affected region were positively correlated (P < 0.001).

**Comparison Between Trigeminal and Thoracic PHN**

The characteristics of pain and sensory abnormalities in subjects with PHN in the trigeminal distribution (n = 20) were compared with those with pain in the thoracic dermatomes (n = 29). The intensities of ongoing pain were similar (6.35 ± 2.01 [trigeminal] vs. 7.5 ± 2.02 [thoracic]), and there were no significant differences in the pain evoked by the dynamic, static, punctate, or pinprick stimuli. In subjects with PHN in a thoracic distribution, thresholds for warmth, coolness, heat pain, and cold pain were increased (P < 0.005) in the affected side compared with the unaffected side. Subjects with trigeminal PHN had lower warmth (P < 0.05) and coolness thresholds (P < 0.005) in the affected side, but the heat pain and cold pain thresholds were similar in the two sides. There were no significant correlations between ongoing pain and allodynia to the mechanical stimuli in either group of subjects. Similarly, the thermal deficits did not correlate with ongoing pain in subjects with trigeminal or thoracic PHN.
Relative Proportion of Patients with Mechanical Allodynia and Thermal Hyperalgesia

In our study population, 14 subjects (22% of all subjects; eight with trigeminal PHN) had both allodynia to cutaneous mechanical stimuli and hyperalgesia induced by thermal stimuli (using the criteria for thermal hyperalgesia of a 1°C difference between affected and unaffected sites). In 52% of subjects (n = 32; nine with trigeminal PHN), mechanical allodynia was associated with normal or elevated thresholds to thermal stimuli. Only 12 subjects (19%; two with trigeminal PHN) had ongoing pain without allodynia or hyperalgesia to mechanical or thermal stimuli. Four subjects (one with trigeminal PHN) had ongoing pain and hyperalgesia induced by heat stimuli, but no allodynia after mechanical stimuli.

Discussion

In this group of 63 adults with PHN, allodynia induced by one or more mechanical stimuli was common. Cutaneous allodynia, in the absence of inflammation, is a sign of central sensitization and is signaled from the periphery by myelinated A fibers. Of note, the intensity of ongoing pain correlated positively with the intensity of allodynia to dynamic mechanical stimulus in subjects with PHN of a duration of less than 1 yr. This correlation was lost in the group with PHN for longer than 1 yr. These findings suggest that activity in cutaneous nociceptors may play an important role in maintaining the central sensitization early in the disease, whereas central mechanisms may prevail even in the absence of peripheral nociceptive input later in the course of PHN. The intensity of allodynia induced by different mechanical stimuli (i.e., static, dynamic, punctate) were correlated, suggesting a common mechanism. Although allodynia to mechanical stimuli was frequent, hyperalgesia to thermal stimuli was uncommon, suggesting that their mechanisms differ.

It has been proposed recently that patients with PHN can be classified into three categories based on their sensory tests and their response to topical therapies. Patients with thermal and mechanical allodynia were postulated to have “irritable nociceptors,” that is, sensitized cutaneous nociceptors. It is postulated that the ongoing activity in the sensitized nociceptors may play an important role in the maintenance of central sensitization. Cutaneous sensibility to thermal stimuli is minimally affected in this subset of patients, who usually experience pain with topical capsaicin and pain relief with topical local anesthetics. A second proposed subset had spontaneous pain, mechanical allodynia, and thermal sensory deficits. Mechanical allodynia in this subset was considered to be secondary to synaptic plasticity or aberrant connections within the dorsal horn of the spinal cord resulting from partial deafferentation. A third category had severe spontaneous pain without cutaneous hypersensitivity. The pain in this subset with marked sensory deafferentation is thought to be caused by spontaneous activity in central neurons as a result of either release of inhibition or hyperactivity of central pain transmission neurons.

In our study, approximately one fourth of the subjects had pain and sensory abnormalities consistent with a mechanism involving sensitized nociceptors. Approximately half of our subjects had sensory abnormalities suggestive of CNS plasticity, and the rest had spontaneous...
ous, but not stimulus-evoked, pain suggestive of central “pain generators.” Our observations are consistent with Baron’s view that, although irritable nociceptors are an important cause of pain in a subset of patients with PHN, the incidence of this may be low compared with pain from degenerative changes resulting in altered central processing.

Nurmikko and Bowsher reported sensory deficits affecting two or more modalities in 39 of 42 patients with PHN, whereas subjects without PHN after zoster had no loss of sensory functions. Morphologic studies have also shown a profound loss of cutaneous nociceptors in patients with PHN. The data support the hypothesis that loss of sensory nerves is associated with the development of pain. Deficits of C-fiber function in PHN patients have also been shown in experiments using topical capsaicin or histamine iontophoresis. These observations led to the hypothesis that central reorganization resulting from sensory deafferentation is the primary pathophysiologic mechanism of PHN. Our data indicating a lack of correlation between intact cutaneous thermal sensation and the intensity of ongoing pain or mechanical allodynia are consistent with this hypotheses. Of note, our finding of the presence of mechanical allodynia without thermal hyperalgesia in a subset of patients with PHN is similar to the sensory changes characteristic of the zone of secondary hyperalgesia that surrounds cutaneous injury or inflammation.

Our observations that mechanical allodynia was often associated with deficits in detection of warmth, coolness, and pain with thermal stimuli in a number of subjects is consistent with earlier reports. A similar lack of correlation between thermal and mechanical hypersensitivity was reported after neuropathic injuries in different strains of mice. Our results differ from those of Rowbotham and Fields in that no significant correlation was found between the magnitude of thermal sensory deficits and the intensity of ongoing pain or allodynia.

This discrepancy may result from differences in patient population and methodology. Rowbotham and Fields excluded subjects with zoster on the head or neck, but we, and Nurmikko and Bowsher, did not. In contrast to patients with PHN in the thoracic dermatomes, patients with trigeminal PHN had no significant alterations in heat and cold pain thresholds in the affected region. Subjects in our study were withdrawn from analgesic therapy for at least 2 weeks before the sensory testing; subjects in the study by Rowbotham and Fields continued to use opioid or tricyclic antidepressant medications. These drugs modulate pain processing in the dorsal horn, and opioids attenuate central sensitization. Another possibility is that the two studies differed in the proportions of patients with an “irritable nociceptor” mechanism versus central mechanisms. We excluded subjects with ongoing pain levels < 4; hence, the average pain scores in our study were higher than in the study by Rowbotham and Fields.

Understanding the different mechanisms that might contribute to pain in PHN may help develop clinical strategies to assess and treat patients with PHN and other neuropathies. For example, in patients with irritable nociceptors, topical local anesthetics might be beneficial, but topical capsaicin may be contraindicated, because the activation of nociceptors might enhance central sensitization. However, the translation of the mechanistic concepts into therapeutic applications may not be simple. Both central and peripheral mechanisms can be involved in a given patient, and therapy may have to be tailored to target the specific mechanisms involved. In time, the treatment of neuropathic pain may come to resemble that of other chronic diseases in which multiple drugs, directed at different mechanisms that contribute to the clinical phenotype, are used.

We observed a difference in the relationship between ongoing pain and allodynia induced by dynamic mechanical stimuli in patients with duration of PHN of ≤ 1 yr and those with a duration > 1 yr. Similar trends were observed for pain induced by pressure and pinprick stimuli. A possible interpretation for our observations is that early in the disease the predominant mechanism for pain is peripheral. Later, central abnormalities may sustain ongoing pain, and anatomic reorganization in the spinal dorsal horn may be responsible for the allodynia. A potential explanation for the epidemiologic observations by Ragozzino et al. that the pain after an acute zoster resolves in less than 1 yr in the majority of patients is that in most patients the peripheral sensitization spontaneously resolves. These observations also imply that there may be a window of opportunity during the first year after shingles during which mechanisms underlying the later stages might be attenuated. In support of this possibility, Bowsher reported that use of amitriptyline during the first 90 days of shingles reduced the prevalence of PHN by half 6–8 months later.

Because of the complexity of the sensory disturbances in PHN, information obtained from quantitative sensory testing on the underlying mechanisms of pain has been
limited. Morphologic data from skin biopsies at PHN sites have shown neurite loss. The discovery of markers for functional subsets of sensory fibers may provide better insights on the class of fibers affected. Functional imaging of the brain has helped localize areas of abnormal brain function in pain patients. Improved resolution may permit visualization of the spinal cord, and perhaps dorsal root ganglia, in the future.

In summary, our study indicates that although PHN has a single well-defined cause, the underlying pathophysiology may vary from patient to patient and with the duration of PHN. Our study suggests not only a complex interplay of peripheral and central mechanisms in the pathophysiology of PHN, but also a mechanism that evolves with time.

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