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ORIGINAL ARTICLE

Pain type and neuropathic pain components in acute herpes zoster

Akut herpes zoster'de ağrı tipi ve nöropatik ağrı bileşenleri

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Summary

Objectives: The aim of this study was to investigate the pain type (nociceptive or neuropathic) and neuropathic pain components in patients with acute herpes zoster (HZ).

Methods: Patients with acute HZ referred to the outpatient Dermatology and Venereology clinic between January 2021 and January 2022 were retrospectively detected. The demographic data including gender and age, rash localization, pain severity, and neuropathic pain components were recorded. Pain severity and neuropathic pain components were evaluated using a Visual Analog Scale (VAS) and Douleur Neuropathique 4 (DN4), respectively.

Results: The study included a total of 58 patients, comprising 33 females and 25 males. Of these patients, 35 (60.3%) were found to have neuropathic pain. Itching, burning, pins and needles, and tingling were the most frequently reported neuropathic pain signs and symptoms. The proportion of female patients with neuropathic pain was found to be significantly higher than that of male patients (p=0.021). No significant differences were observed in the distribution of pain across different body sites or in the age of patients with neuropathic pain (p>0.05). Itching was significantly more common in younger patients (p=0.02).

Conclusion: In conclusion, the study found that over half of the patients with acute HZ experienced neuropathic pain, and this was more frequently observed in female patients. Analysis of different components of neuropathic pain showed significant differences in age, gender, and site distribution. The findings of this study may have important implications for the management and treatment of acute HZ.

Keywords: Herpes zoster; neuropathic pain; nociceptive pain.

Özet

Amaç: Bu çalışmanın amacı, akut herpes zoster (HZ) hastalarında ağrı tipini (nosiseptif veya nöropatik) ve nöropatik ağrı bileşenlerini araştırmaktır.

Gereç ve Yöntem: Ocak 2021 ile Ocak 2022 tarihleri arasında Deri ve Zührevi Hastalıklar polikliniğine başvuran akut HZ'li hastalar retrospektif olarak belirlendi. Cinsiyet ve yaşı içeren demografik veriler, döküntü lokalizasyonu, ağrı şiddeti ve nöropatik ağrı bileşenleri kaydedildi. Ağrı şiddeti ve nöropatik ağrı bileşenleri, sırasıyla Görsel Analog Skala (VAS) ve Douleur Neuropathique 4 (DN4) kullanılarak değerlendirildi.

Bulgular: Çalışmaya toplam 58 hasta (33 kadın, 25 erkek) dahil edildi. DN4 anketine göre, 35 hastada (%60.3) nöropatik ağrı mevcuttu. Kaşıntı, yanma, iğne batması ve karıncalanma, diğer nöropatik ağrı belirti ve semptomlarından daha fazla deneyimlendi. Nöropatik ağrısı olan kadın hasta sayısı, erkek hastalara göre anlamlı olarak fazla saptandı (p=0.021). Döküntü dağılımı veya yaş ile nöropatik ağrı arasında anlamlı farklılık saptanmadı (p>0.05). Kaşıntı, genç hastalarda anlamlı olarak daha fazla saptandı (p=0.02).

Sonuç: Nöropatik ağrı, akut HZ'li hastaların yarısından fazlasında mevcuttu ve kadınlarda daha yaygındı. Yaş, cinsiyet ve döküntü dağılımı açısından bazı nöropatik ağrı bileşenleri arasında farklılıklar mevcuttu. Bu çalışmanın bulguları, akut HZ'nin yönetimi ve tedavisi için yol gösterici olabilir.

Anahtar sözcükler: Herpes zoster; nöropatik ağrı; nosiseptif ağrı.

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Introduction

Herpes zoster (HZ) is a condition characterized by a vesicular rash localized in a unilateral dermatome, resulting from the reactivation of the latent varicella-zoster virus (VZV) in the dorsal root ganglion.[1] Several risk factors have been identified for the development of HZ, including aging, immunodeficiency, female gender, and white race.[2] The increase in the risk of HZ due to aging begins after the age of 50.[3] The risk of HZ increases with age, with the incidence of the disease ranging from 6–8/1000 person-years at age 60 to 8–12/1000 person-years at age 80.[3] The lifetime risk of developing HZ is 25–30%, rising to 50% over the age of 85.[4] HZ pain occurs in three stages: acute herpetic neuralgia within one month of the onset of the rash, subacute herpetic neuralgia lasting for 1–3 months, and postherpetic neuralgia with pain lasting for ≥3 months.[5,6] Reactivation of VZV in the dorsal root ganglia causes neuronal damage, stimulation of nociceptors, and initiation of inflammatory processes, resulting in cutaneous neural dysfunction and peripheral tissue inflammation.[7] During the acute phase of HZ, nociceptive and neuropathic pain develop through different pathways, and the location, duration, and intensity of different types of pain and sensory symptoms can vary greatly among patients.[5,8] HZ pain and sensory symptoms can have a significant negative impact on the functional status and quality of life of affected individuals.[9] While many studies have investigated neuropathic pain in postherpetic neuralgia, few have examined neuropathic pain components in acute HZ.[4,8] Therefore, this study aimed to determine the frequency of neuropathic pain and its components in patients presenting with acute HZ.

Material and Methods

Study Design and Population

Local Ethics Committee approval was obtained for this study (Decision no: 60-60-03). This study was conducted in accordance with the Declaration of Helsinki. The medical records of patients diagnosed with acute herpes zoster between January 2021 and January 2022 at the outpatient Dermatology and Venereology clinic in a tertiary hospital were retrospectively evaluated. Inclusion criteria included patients with a physician-confirmed diagnosis of acute HZ, aged between 18 and 80 years old, who completed the Visual Analog Scale (VAS) and Douleur Neuropathique 4 (DN4) questionnaires. Exclusion criteria were the presence of recurrent HZ and treatment with neuropathic pain medications. All patient files were examined for demographics including age and gender, onset and localization of skin rash, and presence of pain.

Data Collection

A retrospective data analysis was performed, comprising comprehensive data for demographics including age and gender, onset and localization of skin rash, presence of pain, comorbid diseases, and VAS and DN4 questionnaires.

VAS is used to measure pain intensity on a 10 cm line ranging from 0 (no pain) to 10 (most severe pain), with patients marking their corresponding pain intensity. DN4 is a questionnaire used to assess neuropathic pain, consisting of a symptom questionnaire and clinical examination. Each "yes" answer is given 1 point, with ≥4 points indicating the presence of neuropathic pain. The questionnaire allows for a maximum score of 10 points and covers symptoms such as burning, painful cold, electric shocks, tingling, pins and needles, numbness, and itching, as well as hypoesthesia to prick and touch and allodynia.[10] DN4's Turkish adaptation, validity, and reliability study was conducted by Unal-Cevik et al.[11]

Statistical Analysis

The data were evaluated using the SPSS (version 22.0) IBM SPSS statistical package program. Arithmetic mean and standard deviation values are given for variables obtained by measurement that show normal distribution. Median and Interquartile Range (IQR) are given for variables that do not show normal distribution. Variables indicated by counting are shown as numbers and percentages. The Shapiro-Wilk test was used to assess normal distribution. Analysis of variance was used for those with normal distribution. Bonferroni out of post-hoc tests was used for pairwise comparisons. The Kruskal-Wallis test was used to compare multiple groups that did not show normal distribution. The Mann-Whitney U test was used for pairwise comparisons. Values with $p<0.05$ were accepted as statistically significant.

Results

During the retrospective evaluation period, 87 patients were diagnosed with acute HZ. 19 patients who did not meet the inclusion-exclusion

Table 1. Neuropathic pain components according to gender

	Female (n=33)		Male (n=25)		
DN4 components	**Yes**	**No**	**Yes**	**No**	**p**
Burning	23	10	14	11	0.29
Painful cold	13	20	3	22	**0.02**
Electric shock	15	18	3	22	**0.01**
Tingling	24	9	13	12	0.11
Pin and needles	23	10	14	11	0.29
Numbness	13	20	7	18	0.37
İtching	21	12	16	9	0.98
Allodynia	19	14	11	14	0.31
Hypoesthesia to touch	8	25	5	20	0.70
Hypoesthesia to pinprick	3	30	2	23	0.89

Mann Whitney U test, statistical significance was set to p<0.05. DN4: Douleur neuropathique 4.

criteria and 10 patients with incomplete data were excluded. As a result, the medical records of 58 patients were reviewed retrospectively. The mean age was 58.79±15.55 years, ranging from 19 to 80 years. VAS scores (median [min–max]) were 6.0 (2.0–10.0) in females and 5.0 (0.0–9.0) in males. No statistically significant difference was found between genders (p=0.173). The number of patients with neuropathic pain, as assessed by the DN4, was 35 (60.3%). The overall DN4 scores (median [min–max]) were 4.0 (0.0–10.0). Neuropathic pain was present in 14 male and 21 female patients. There was a significant difference in the neuropathic pain rate between male and female patients (p=0.021).

Based on responses to the DN4 questionnaire, the primary symptoms in patients were itching, burning, pins and needles, and tingling (experienced by 63.8%). Allodynia, numbness, electric shocks, and painful cold were reported by 51.7%, 34.5%, 31.0%, and 27.6% of the patients, respectively. Touch hypoesthesia and needle hypoesthesia, among the symptoms in the DN4 questionnaire, were detected in 22.5% and 8.6% of the patients, respectively, and these symptoms were the least common neuropathic pain components. Painful cold and electric shock were statistically higher in female patients than in males (p=0.022, p=0.007, respectively). There was no statistically significant difference between genders in other symptoms and markers of neuropathic pain, as shown in Table 1.

Thirty (51.7%) of the patients were >60 years old. When evaluating the age distribution and pain intensity, the median VAS was 4.50 (min–max: 0.0–10.0) in patients >60 years old and 6.0 (min–max: 2.0–10.0) in those <60 years old. There was a positive correlation between age distribution and VAS (r=.249), however, the difference was not significant (p=0.060). Neuropathic pain symptoms by age distribution are given in Table 2.

The most common site distribution was in the thoracic region (79.3%). Herpes zoster was localized in the lower extremity in 8.6% of the patients, in the upper extremity in 6.8%, and in the ophthalmic region in 5.1% of the patients. There was no statistically significant difference between site distribution and VAS (p=0.703) and DN4 score (p=0.588). No statistical difference was found in neuropathic pain symptoms according to site distribution, except for pinprick hypoesthesia (Table 3).

Discussion

This study assessed the demographic and clinical characteristics of patients with acute herpes zoster (HZ). Among the evaluated HZ patients, over 55% were female, and the incidence of neuropathic pain was 60.3%, with females being more commonly affected. Additionally, pain severity and neuropathic pain increased with age. While previous studies have associated female gender with an increased incidence of HZ, the evidence indicates that there is no difference in the incidence and severity of herpes

Table 2. Neuropathic pain components according to age

	Age <60 yr (n=28)		Age ≥60 yr (n=30)		
DN4 components	**Yes**	**No**	**Yes**	**No**	**p**
Burning	15	13	22	8	0.12
Painful cold	7	21	9	21	0.67
Electric shock	6	22	12	18	0.13
Tingling	16	12	21	9	0.31
Pin and needles	18	10	19	11	0.94
Numbness	10	18	10	20	0.85
İtching	22	6	15	15	**0.03**
Allodynia	11	17	19	11	0.07
Hypoesthesia to touch	9	19	4	26	0.09
Hypoesthesia to pinprick	1	27	4	26	0.19

Mann Whitney U test, statistical significance was set to p<0.05. yr: Years old; DN4: Douleur neuropathique 4.

Table 3. Neuropathic pain components according to site distribution

	Site distribution				
DN4 components	**Upper extremity n=4**	**Thoracal region n=46**	**Lower extremity n=5**	**Head and face n=3**	**p**
Burning	4	28	3	2	0.49
Painful cold	0	14	2	0	0.36
Electric shock	0	16	2	0	0.31
Tingling	1	31	4	1	0.21
Pin and needles	2	31	2	2	0.62
Numbness	2	16	2	0	0.56
İtching	2	30	3	2	0.94
Allodynia	2	22	4	2	0.55
Hypoesthesia to touch	0	9	3	1	0.14
Hypoesthesia to pinprick	0	2	2	1	**0.02**

Statistical significance was set to p<0.05. DN4: Douleur neuropathique 4.

zoster between men and women.[1,12] In this study, no difference between genders in pain severity was observed, but neuropathic pain was found to be statistically higher in women than in men. This discrepancy may have developed due to the small size of our patient population.

Bouhassira et al.[4] reported that 61.8% of patients developed neuropathic pain in acute HZ, and the mean DN4 value was 4.2±1.91. Patients over 50 years of age were included in their study, and the frequency of neuropathic pain was found at a rate similar to our results. Burning, allodynia, and tingling symptoms in the DN4 questionnaire were associated with acute HZ in 79.8%, 71.4%, 64.1%, and 58.0% of patients, respectively. In our study, burning, and tingling were present in 63.8% of the patients. Haanpää M et al.[13] stated that almost half of the patients suffered from allodynia, which occurs due to central sensitization. In the study by Kramer S et al.,[7] which investigated somatosensory changes in acute shingles, pain provoked by pressure, burning pain, pins and needles, and tingling were found in 77.9%, 75%, 73.5%, and 63.3% of the patients, respectively. In the same study, squeezing pain and electric shock-like pain were seen in 35.3% of the patients. Neuropathic pain components were generally detected more frequently in their patient population than in ours. The

researchers argued that the determined sensorial signs develop due to central sensitization and deafferentation in acute HZ.[7]

Central sensitization is defined as increased responsiveness of nociceptive neurons in the central nervous system to afferent stimuli. Pain sensations are normally induced by C- and Aδ-fibers.[14] As peripheral nerve damage and inflammation occur in the HZ, C-fiber loss develops and pain sensation is transmitted by A-fibers.[13,14] In addition, due to the damage caused by HZ, N-methyl-D-aspartate (NMDA) release develops from spinal cord dorsal horn neurons by creating discharge in axonal membranes. Sensory stimuli get an amplified response in the spinal cord.[15] Painless tactile stimuli become able to activate spinal cord pain signalling neurons via Aδ and Aβ-low-threshold mechanoreceptors.[14]

There is no study in the literature evaluating the difference between neuropathic pain components in HZ in terms of gender. Painful cold and electric shock pain were more common in women in our study. This may be due to the higher number of female gender in our study. The other remarkable result in our study was that itching was more common in those younger than 60 years of age. There are few studies evaluating itch in acute HZ. Ishikawa R et al.[16] determined the frequency of itch to be 63% in the first month, similar to our findings. The researchers stated that the frequency of itching was similar between age groups. In another study, itching was reported in 70.8% of 661 HZ patients. In this study, it was stated that there was no difference between age groups. Unlike the patient population in our study, patients older than 50 years of age were evaluated in this study.[17] There are different theories about the mechanism of itching in shingles. It has been stated that itching may occur due to the transmission of low-threshold signals by the myelinated C fibers, and in addition, itching occurs through a special pathway between the skin and the thalamus.[16] The other theory states that itching develops due to histamine release in acute HZ, while neuropathic itch develops as a result of neuropathic pain secondary to neural injury and demyelination in the chronic phase.[18] Itching could be due to the transmission of stimuli to the spinal cord by low-threshold mechanoceptors such as allodynia.[19]

Thoracic dermatomes are the most common involvement in HZ and this rate has been found up to 58.9% in studies.[20] In our patient population, however, a higher rate of thoracic involvement was detected. Although hypoesthesia to pinprick was observed to be statistically higher in the lower extremity, it is difficult to interpret because the number of patients is small.

The pain associated with acute HZ has a significant impact on an individual's quality of life and ability to function.[21] Severe and neuropathic pain during this phase increase the risk of developing postherpetic neuralgia, a complication of HZ.[4,22] However, studies have conflicting results regarding the effectiveness of gabapentin in preventing the development of postherpetic neuralgia during the acute phase.[23] As patients with acute HZ typically present with skin lesions, they are commonly referred to dermatology outpatient clinics. It is crucial for dermatologists to be familiar with the components of neuropathic pain and to identify the patient groups in which neuropathic pain is more prevalent. Therefore, defining the type of pain experienced during acute HZ and arranging appropriate treatment is crucial.

Our study has several limitations, such as having a small patient population, being retrospective, and single-center in design.

Conclusion

It is known that neuropathic pain develops in the majority of patients with acute HZ, and the results of our study confirm this situation. Itching, burning, pins and needles, and tingling are the most common neuropathic pain components. Also, there are differences between neuropathic pain components in terms of age, gender, and site distribution. The exact mechanism by which neuropathic pain components appear at different frequencies in acute HZ has not been identified.

Ethics Committee Approval: The Uşak University Clinical Research Ethics Committee granted approval for this study (date: 06.04.2022, number: 60-60-03).

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