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ORIGINAL ARTICLE

Evaluation of the Demographic and Clinical Characteristics of Patients Diagnosed with Herpes Zoster

Herpes Zoster Hastalarının Demografik ve Klinik Özelliklerinin Değerlendirilmesi

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ABSTRACT

Background: Herpes zoster is a disease that is more frequently seen in people aged over 50 years and negatively affects the quality of life due to the development of post-herpetic neuralgia. This study aimed to investigate the demographic and clinical characteristics of patients diagnosed with herpes zoster.
Methods: In this cross-sectional study, the data of patients who were followed up with a diagnosis of herpes zoster at the dermatology department between 2013 and 2020 were retrospectively examined.
Results: Of 440 patients, 252 (57.3%) were female and 188 (42.7%) were male. The mean age was 48.9±18 (4-94) years. The most common localization was the thoracic region at a rate of 35.5% and the lumbar region at a rate of 21.4%. Disseminated and ophthalmic zoster were more common in elderly patients (p<0.001). The most common comorbidities were hypertension (HT)+coronary artery disease (CAD) (12.6%), cancer (10.3%), and diabetes+HT (5.9%). Severe pain was observed in 19.7% of the patients and was more common in women (p=0.016). The rate of moderate and severe pain was high in the patients with HT+CAD and cancer (p<0.001). Post-herpetic neuralgia was observed in 15.3% of the patients aged over 50.
Conclusions: Herpes zoster is especially common in adults. Since it causes acute pain and can lead to postherpetic neuralgia development, risky patient groups should be more carefully followed up and treated.

Keywords: herpes zoster, clinical features, postherpetic neuralgia

ÖZ

Amaç: Herpes zoster 50 yaş üzerinde daha sık görülen ve post herpetik nevralji gelişmesi nedeniyle yaşam kalitesini etkileyen bir hastalıktır. Bu çalışmada herpes zoster tanısı almış hastaların demografik ve klinik özelliklerinin incelenmesi amaçlanmıştır.
Yöntem: Bu kesitsel çalışmada dermatoloji bölümünde 2013-2020 yılları arasında herpes zoster tanısı ile izlenen hastaların verileri geriye dönük olarak incelendi.
Bulgular: 440 hastanın 252'si (%57,3) kadın, 188'i (%42,7) erkekti. Yaş ortalaması 48,9±18 yıl (4- 94 yıl) idi. En sık yerleşim bölgesi %35,5 oranında torakal bölge ve ikinci sırada %21,4 oranında lomber bölgeydi. Dissemine tutulum ve oftalmik zona ileri yaştaki hastalarda daha sık görüldü (p<0,001). Komorbiditeler arasında en sık saptananlar %12,6 oranı ile hipertansiyon ve koroner arter hastalığı birlikteliği, %10,3 ile kanser, %5,9 diyabet ve hipertansiyon birlikteliğiydi. Şiddetli ağrı hastaların %19.7'sinde izlendi ve kadınlarda daha sıktı (p=0.016). HT+KAH grubunda ve kanser hastalarında orta ve şiddetli ağrı oranı yüksekti (p<0.001). 50 yaş üzerindeki hastaların %15,3' ünde post herpetik nevralji izlendi.
Sonuç: Herpes zoster özellikle yetişkinlerde sıklıkla görülmektedir. Akut ağrı oluşturması ve postherpetik nevralji gelişebilmesi nedeniyle, özellikle riskli hasta gruplarının takip ve tedavisine önem gösterilmesi gerekmektedir.

Anahtar Kelimeler: herpes zoster, klinik özellikler, postherpetik nevralji

Introduction

Herpes zoster (HZ) is a disease characterized by a painful vesicular rash, usually located unilaterally, which develops due to the reactivation of the varicella-zoster virus. After an individual has chickenpox, the varicella-zoster virus is hidden in the dorsal root ganglia or the sensory ganglia of the cranial nerves (1,2). Generally, following any situation affecting the immune system, the virus reactivates again to form HZ. The disease is most common in adults and the elderly. Even if HZ improves, there is a risk of developing post-herpetic neuralgia (PHN), and therefore the disease can cause morbidities (1,2).

Objectives

In this study, we aimed to investigate the demographic and clinical characteristics of patients followed-up with the diagnosis of HZ, identify seasonal characteristics of HZ, examine accompanying comorbidities, determine treatment options and whether they developed PHN, and explore the relationship between demographic and clinical features and PHN.

Methods

The patients who were followed up with the diagnosis of HZ at the dermatology department of our hospital

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between 2013 and 2020 were retrospectively scanned. Approval was obtained from the ethics committee of our hospital with the number 2021/21.

The study included a total of 440 patients diagnosed with HZ. The patient's demographic characteristics, disease duration, disease characteristics, symptoms at the time of diagnosis, localization of lesions, clinical severity, accompanying systemic diseases, characteristics of treatments given, and PHN development status were examined. In the clinical evaluation of pain, the Numerical Rating Scale was used, and scores were evaluated as 0, no pain; 1-3 mild pain, 4-6, moderate pain, and 7-10, severe pain (3). PHN was accepted as the persistence of pain after three months following the diagnosis of HZ.

Data collected from the patients were analyzed using the Statistical Package for the Social Sciences v. 25 (SPSS for Windows v. 25, Chicago, Illinois, USA) software package program. When summarizing data obtained from the study, for continuous (numerical) variables, descriptive statistics were tabulated as mean ± standard deviation or median, minimum, and maximum values depending on the distribution of data. Categorical (discrete) variables were summarized as numbers and percentages. The normality of the distribution of numerical variables was checked using the Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests. Student's t-test was used to compare two groups in terms of normally distributed continuous variables. The chi-square test was conducted to compare data of a discrete variable structure. The statistical results were evaluated at the 95% confidence interval and the significance level of $p < 0.05$.

Results

Of the 440 patients diagnosed with HZ, 252 (57.3%) were female and 188 (42.7%) were male, and the female/male ratio was 1.34. The mean age was 48.9 ± 18 (4-94) years in all patients; 50.3 ± 18.6 years in the women, and 47 ± 17 years in the men. In the distribution of patients according to age ranges, the most common age range was the sixth decade (51-60 years) at a rate of 22%, followed by the fourth decade (31-40 years) at 18.9% and the seventh decade (61-70 years) at 15.5% (Table 1).

Table 1. Distribution of herpes zoster cases according to age decade, n: number

Age range (decade)	n	%
0-10	4	0.9
11-20	20	4.5
21-30	50	11.4
31-40	83	18.9
41-50	66	15.0
51-60	97	22.0
61-70	68	15.5
71-80	36	8.2
81-90	15	3.4
Total	440	100

Considering the seasonal distribution, the frequency of HZ did not show a statistically different distribution between the months and between the seasons (winter, 26.6%; spring, 24.5%; summer, 23.2%; and autumn, 25.7%) (Table 2).

Table 2. Monthly distribution of herpes zoster cases, n: number

Month	n	%
January	35	8,0
February	38	8,6
March	34	7,7
April	31	7,0
May	43	9,8
June	29	6,6
July	28	6,4
August	45	10,2
September	43	9,8
October	46	10,5
November	24	5,5
December	44	10
Total	440	100

When the distribution of comorbidities was examined, no comorbidity was found in 214 (48.9%) of the 438 patients (missing data of 2 patients), and the most common comorbidity was hypertension (HT) + coronary artery disease (CAD) at a rate of 12.6%. This was followed by cancer at 10.3%, diabetes mellitus (DM) + HT at 5.9%, and DM + psychiatric disease at 3.9% (Table 3).

Table 3. Distribution of comorbidities, n: number

Systemic diseases	n	%
Anemia	8	1.8
DM	17	3.9
DM + HT	26	5.9
HT + thyroid disease	4	0.9
HT + DM + psychiatric disease	8	1.8
HT + CAD	55	12.6
Cancer	45	10.3
Organ transplantation	3	0.7
Psychiatric disease	17	3.9
Rheumatoid disease	12	2.7
Thyroid disease	11	2.5
Other	18	4.1
None	214	48.9
Total	438	100
Missing	2	

HT: hypertension, DM: diabetes mellitus, CAD: coronary artery disease

When the patients with cancer were evaluated, 23 of the 45 patients had hematological malignancies and 22 had solid organ malignancies. Of the patients, 22 were receiving chemotherapy, two were receiving radiotherapy, and one was receiving chemoradiation. Seven patients had undergone

allogeneic bone marrow transplantation and were receiving immunosuppressive therapy. Thirteen patients were not receiving chemotherapy or radiotherapy. In addition, three patients who had undergone organ transplantation and 10 of the 12 patients with rheumatological diseases were receiving immunosuppressive therapy.

Of all the patients, 228 (52.1%) did not use additional drugs, 57 (13%) were using a single drug, and 53 (34.9%) were using multiple drugs.

The median disease duration was 4 days (range, 1-21 days). The most common symptom accompanying the rash was pain in 385 (87.5%) patients, itching in 27 (6.1%), burning in 14 (3.1%), fever in 10 (2.2%), and numbness in one (0.2%). The most common localization was the thoracic region at a rate of 35.5%, followed by the lumbar region at 21.4%. When the relationship between lesion localization and patient age was examined, ophthalmic and disseminated zoster were mostly in the elderly patient while lumbar involvement was more common in the younger group, and this relationship was statistically significant ($p < 0.001$). There was no significant difference in localization according to gender (Table 4).

HZ was found on the left side in 53% of the 355 patients and the right side in 47% (missing data of 85 patients). There was no significant difference in the lesion side according to age and gender. The most common clinical presentation of the rash was dermatomal vesicular lesions in 397 patients (90.4%), dermatomal crusted lesions in 25 (5.7%), disseminated vesicular lesions in nine (2.1%), dermatomal necrotizing ulcerated lesions and vesicular lesions in five (1.1%), and multi-dermatomal vesicular lesions in three patients (0.7%).

Pain was not detected in 10.7% of the 431 patients (missing data of 9 patients); mild pain was detected in 26.9%, moderate pain in 42.7%, and severe pain in 19.7%. There was no relationship between pain severity and seasonal distribution, localization, affected side, and clinical presentation. In the group without pain, the rate of male patients was higher, and the mean age was lower while there were more female patients in the severe pain group ($p = 0.040$, $p < 0.001$, and $p = 0.016$, respectively). In terms of comorbidities, patients with HT + CAD and those with cancer were more commonly seen in the moderate and severe pain groups, and the rate of those who did not use additional drugs was lower in the group with severe pain ($p < 0.001$) (Table 5).

Table 4. Relationship between lesion localization and patient age, n: number, statistically significant results presented in bold

Lesion localization	n	%	Mean age (years)
Lower extremity	27	6.1	50.85
Disseminated	8	1.8	**63.37**
Zoster duplex	3	0 .7	61.00
Intraoral	2	0 .5	23.50
Cranial	20	4.5	46.55
Lumbar	94	21.4	**44.18**
Ophthalmic	25	5.7	**60.72**
Sacral	36	8.2	48.33
Cervical	34	7.7	47.52
Thoracal	156	35.5	48.02
Upper extremity	35	8.0	56.37
Total	440	100	
p-value			<0.001

Of the 440 patients, 419 were treated as outpatients and 21 as inpatients. The inpatient group consisted of ophthalmic (n = 13) and disseminated zoster (n = 8) cases, and all received parenteral acyclovir

Table 5. Relationship between pain and clinical characteristics, n: number, statistically significant results presented in bold

Pain	n (%)	Female/Male (n)	Mean Age (years)	HT + CAD (n)	Cancer (n)	Additional drug use (none/single/multiple) (n)
None	46 (10.7)	**20/26**	**37.91**	3	1	33/2/11
Mild	116 (26.9)	71/45	42.58	5	7	67/18/31
Moderate	184 (42.7)	99/85	50.83	**24**	**20**	96/22/65
Severe	85 (19.7)	**59/26**	**59.44**	**22**	**17**	**26**/15/43
Total	431 (100)	249/182	48.93	54	45	429
p-value		0.040./ 0.016	<0.001	<0.001	<0.001	<0.001

Table 6. Relationship between pain treatment and clinical characteristics, NSAIDs: non-steroidal anti-inflammatory drugs, n: number, statistically significant results presented in bold

Pain treatment	n (%)	Mean age, (years)	Comorbidity	Additional drug use
None	57 (13)	**38.80**		None
NSAIDs/Acetaminophen	320 (72.7)	**48.61**	None/psychiatric disease	Single drug
Gabapentin	59 (13.4)	**59.61**	HT + CAD/cancer	
Other	4 (0.9)	59.25		
Total	440 (100)	48.90		
p-value		<0.001	<0.001/<0.043	<0.001/<0.002

treatment. In the whole sample, valacyclovir was used in 73% of the patients, brivudine in 15%, and acyclovir in 5.2%. In addition, 47.6% of the patients who were given antiviral treatment received antiviral treatment within the first 72 hours. Antiviral treatment was not applied to 6.8% of the patients, the majority of whom were children and young patients.

In the treatment of pain, non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen were used in 72.7% of the patients, gabapentin in 13.4%, and other drugs (amitriptyline or carbamazepine) in 0.9%. Thirteen percent of the patients did not receive pain treatment. There was no relationship between pain treatment and season, localization, affected side, and gender. There were more elderly patients in the group that took NSAIDs or acetaminophen compared to the group that did not take pain treatment and the group receiving gabapentin and those receiving NSAIDs or acetaminophen ($p < 0.001$). In terms of comorbidities, the use of NSAIDs or acetaminophen was higher than that of gabapentin in the group without comorbidities and in the group with psychiatric diseases ($p < 0.001$ and $p < 0.043$, respectively). The number of patients who did not receive pain treatment was higher in the group that did not use additional drugs ($p < 0.001$), while the use of NSAIDs or acetaminophen was found higher than gabapentin in those that used a single drug ($p < 0.002$) (Table 6).

Among the complications, PHN was observed in 13 (4.7%) of the 275 patients with a long-term follow-up. When the patients aged 50 and over (n = 78) were evaluated, PHN was observed in 12 (15.3%) of these patients. There was no relationship between the development of PHN and gender, localization, season, affected side, early initiation of antiviral treatment, and antiviral type. However, the development of PHN was more frequently observed in patients aged over 50 years ($p < 0.001$), those with severe pain ($p < 0.001$), and those with the comorbidities of HT/DM/psychiatric disease ($p < 0.001$) and less frequently observed in those that did not use additional drugs due to any other disease ($p < 0.013$). Lastly, two patients were with Ramsay Hunt syndrome, and two of the 25 patients were with ophthalmic zoster had keratitis.

Conclusions

Although HZ can be seen at all ages, it is an infectious disease with an increased incidence especially after the age of 50 years. The most common complication of the disease is PHN, which can occur despite the many treatment options available for HZ. The incidence of HZ has been reported as 3-5/1.000 person-years in North America, Europe, and Asia-Pacific, and studies suggest an increasing incidence in recent years (4,5). In a recent article in which 69 studies were reviewed, the worldwide incidence of HZ was 5.23-10.9/1,000 person-years among patients aged over 50 years (6).

In our study, the number of female patients was higher than that of male patients. While many studies have similarly found that HZ is more common in women (2,5,7,8), there are also others reporting a higher incidence in men (9-11). In a meta-analysis evaluating risk factors, HZ was determined higher in women in most of the 27 studies examining the gender ratio (12). In a review in which HZ was evaluated in India, 21 of the 26 studies reported a higher rate of male patients and five found a higher rate of female patients (13). Due to the different results in these studies, the relationship between HZ and gender is yet to be fully elucidated.

The incidence of HZ increases with age (1,2,8). In a population-based study conducted in Korea, it was found that the frequency of HZ increased with age, was most common in those aged 50-59 years, and decreased over the age of 80 years. In addition, it was shown that the rate of hospitalization of patients increased with increasing age (7). In a recent review, it was observed that the incidence of HZ increased with age in all the studies reviewed while some reported a decrease in HZ in patients of advanced age (≥70, ≥75, ≥80, and ≥85 years) (6). In the current study, HZ was most common in the sixth decade of life (51-60 years), and a significant decrease was observed in the frequency of the disease over the age of 80 years.

While some studies have found that HZ is more common in summer months (9,10,14,15), others have shown no seasonal difference (5,7,16). In three different studies conducted in Turkiye, more cases were found in December and winter, in January and August, and in March, but there was no statistical significance (2,17,18). In a study conducted by Hayran et al. evaluating 3.856 patients, no seasonal differences were observed in all patients, but those with ophthalmic zoster presented more frequently in autumn (19). In our study, no statistical difference was detected in the number of cases in terms of seasonal distribution. Further studies to be conducted with larger case series in Turkiye will contribute to the data related to the seasonal variation of the disease.

In this study, when the diseases accompanying HZ were examined, the HT + CAD comorbidity group ranked first, followed by cancer, DM + HT, and DM + psychiatric disease. The majority of the patients in the psychiatric diseases group had depression and anxiety disorders. In addition, the majority of rheumatological diseases consisted of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).

In a study investigating risk factors for HZ, patients with a history of bone marrow or stem cell transplantation were found as the highest risk group for HZ. This was followed by with a history of solid organ transplantation, HIV infection, and SLE in that order. In addition, a higher incidence was found in those who received chemotherapy or immunosuppressive treatment compared to those that did not receive these treatments (20). In another study, when patients aged over 65 years were examined, the incidence of HZ was significantly higher in those with cancer, and it was also higher in hematological cancers than in solid organ cancers (21). In our study, the patients with hematological malignancies and solid cancers were almost equal in number, and the majority of these

patients were receiving immunosuppressive therapy or chemotherapy.

In a meta-analysis examining risk factors, it was stated that autoimmune diseases (RA and SLE), inflammatory bowel disease, DM, chronic kidney disease, chronic obstructive pulmonary disease, depression, and asthma posed an increased risk for HZ (12). In a study conducted in Thailand in 2022, the incidence of HZ was 3.96/person-year in patients with DM, and HT was revealed as an independent risk factor (22). In another study investigating the incidence of HZ in patients with RA, risk factors for HZ were HT and dyslipidemia independent of antirheumatic therapy, gender, and age (23). The most common comorbidities in our study were consistent with these literature data. There was no immunosuppression or comorbidity in pediatric patients.

Considering the clinical characteristics of HZ, the most common clinical presentation is vesicular lesions with dermatomal localization, and the most common localization is the thoracic region (1,2,13,17,18,24,25). Similarly, in our study, the most common localization was the thoracic region, while ophthalmic and disseminated involvements were more common in the elderly patients and lumbar involvement in the younger patient group. In the pediatric patient group (0-18 years), the most common localization was the thoracic and lumbar regions.

Pain is the most disturbing symptom of HZ, and its early treatment is important to reduce the risk of PHN development. In addition, prolonged pain leads to a loss in daily activities and a decrease in quality of life (26,27). In our study, female patients had more severe pain, and moderate to severe pain was more common in the HT + CAD and cancer groups. In the group in which no pain was detected, the male gender and a lower mean age were predominant. It has been stated that both acute pain and PHN decrease in patients who start antiviral treatment within the first 72 hours of developing a rash (4). However, patients need pain management despite receiving antiviral treatment (27).

In our study, while NSAIDs or acetaminophen were used most frequently in the treatment of acute pain in HZ, gabapentin was initiated in patients with severe pain and cases for whom analgesics were not sufficient. Although gabapentin is used especially in PHN, it provides acute pain control in the majority of patients with severe pain. Most pediatric patients did not need pain treatment. In parallel with the clinical severity of pain, there were more elderly patients in the group that took NSAIDs or acetaminophen compared to the group that did not take analgesics and in the group taking gabapentin and those taking NSAIDs or acetaminophen. Additional drug use was also a factor that increased the need for pain treatment.

In the current study, PHN was observed in 13 (4.7%) of 275 patients (only data of patients with long-term follow-up). Pain that persisted three months after recovery from HZ was evaluated as PHN. In a study from the UK, the incidence of PHN1, defined as persisting pain at least one month after recovery from HZ, was determined as 19.5%, and that of PHN3, defined as persisting pain for three months after recovery from HZ, was 13.7% in patients aged over 50 years (28). In another study conducted in Italy, PHN1 was reported as 9.4% and PHN3 as 7.2% in immunocompetent individuals with HZ over 50 years of age (29). In another study from Italy evaluating patients aged over 50 years, the incidences of PHN1 and PHN3 were 22.7% and 12.7%, respectively (8). In our study, the incidence of PHN was lower because the mean age of the patients with a longer follow-up was below 50 years (mean age: 41.6 years, n: 275), PHN was not seen in the pediatric group, and the number of elderly patients was low. When the patients over 50 years were evaluated separately, PHN was observed in 15.3% of these patients, and this rate was statistically significantly higher compared to the remaining age groups. The incidence of PHN increases with age, and it has been shown that factors causing the development of PHN are the presence of prodromal pain, the severity of rash, severe pain, advanced age, and immunocompromised conditions. In addition, it has been reported that PHN is more common in women, diabetic patients, and ophthalmic shingles (30). In the current study, PHN was statistically significantly higher in patients over 50 years of age, those with severe pain, and the HT + DM and psychiatric diseases groups. No significant difference was found in terms of gender, lesion localization, and the presence of early antiviral treatment.

The limitations of our study are that it has a single-center retrospective nature and the inability to follow up PHN in all patients.

Although HZ can be seen at any age, it can cause complications especially in elderly individuals. The data obtained from our study are consistent with those reported by previous studies. However, unlike the literature, we determined that the incidence of HZ did not significantly differ according to gender and season. Especially elderly and immunosuppressive patients with HZ need to be carefully treated and followed up in terms of pain management and PHN development.

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