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Evaluation of Demographic and Clinical Data of Herpes Zoster Patients Admitted To Tertiary Referral Dermatology Clinic During COVID-19 Pandemic

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Abstract

Background: Herpes zoster infection (shingles) occurs due to reactivation of the varicella zoster virus (VZV) usually contracted during childhood. Dermatomal involvement is characterized by vesicular rash. Symptoms such as pain and itching are usually present. Complications may be life-threatening and/or result with sequelae. Psychogenic factors and/or other underlying systemic diseases may provoke reactivation of VZV. Coronavirus disease (COVID-19) infection is one such factor.

Objectives: The aim of this study is to evaluate the demographic and clinical data collected from patients admitted to our tertiary referral medical center and diagnosed with herpes zoster during the COVID-19 pandemic.

Methods: Six hundred and sixty-one patients admitted to our hospital and diagnosed with herpes zoster between October 2020 and October 2021 were included in the cross-sectional retrospective study.

Results: The age range was between 1 and 90, and the mean age was 50.4±19.9 years. Fifty percent were female and 50% were male. Complications were found in 62% of the patients, and 54% had postherpetic neuralgia. A history of an additional comorbidity was found in 79% of the patients. It was observed that 10% of the patients were hospitalized, and their mean age was 66.26±14.4 years. Three percent of the patients had an association with COVID-19 vaccine/infection.

Conclusion: Our study is unique because it includes both pediatric and adult patients. Also significant for providing one-year demographic data for shingles during the COVID-19 era.

Key words: Acyclovir, COVID-19, herpes zoster, neuralgia

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COVID-19 Pandemisi Sırasında Üçüncü Basamak Hastaneye Başvuran Herpes Zoster Hastalarının Demografik ve Klinik Verilerinin Değerlendirilmesi

Öz

Giriş: Herpes zoster enfeksiyonu (zona), genellikle çocukluk döneminde bulaşan varisella zoster virüsünün (VZV) yeniden aktivasyonu nedeniyle oluşur. Dermatomal tutulum veziküler döküntü ile karakterizedir. Ağrı ve kaşıntı gibi semptomlar genellikle mevcuttur. Komplikasyonlar yaşamı tehdit edici olabilir ve/veya sekel ile sonuçlanabilir. Psikojenik faktörler ve/veya altta yatan diğer sistemik hastalıklar bu virüsün yeniden aktivasyonunu tetikleyebilir. Coronavirus hastalığı (COVID-19) enfeksiyonu da bu faktörlerden biri olabilir.

Amaç: Bu çalışmanın amacı, üçüncü basamak merkezimize başvuran ve COVID-19 pandemisi sırasında herpes zoster tanısı konan hastalardan toplanan demografik ve klinik verileri değerlendirmektir.

Yöntemler: Kesitsel retrospektif çalışmanın verileri üçüncü basamak merkezimiz Dermatoloji Kliniği'nden elde edildi. 1 Ekim 2020 ile 1 Ekim 2021 tarihleri arasında herpes zoster tanısı dermatoloji hekimlerimiz tarafından konulmuş veya desteklenmiş olan 661 hasta çalışmaya dahil edildi.

Bulgular: Yaş aralığı 1 ile 90 arasında olup, yaş ortalaması 50.4±19.9 yıl idi. Katılımcıların %50'si kadın, %50 erkekti. Hastaların %62'sinde komplikasyon saptandı, %54'ünde postherpetik nevralji vardı. Hastaların %79'unda ek bir komorbidite öyküsü bulundu, %10'unun hastanede yattığı ve yaş ortalamalarının 66.26±14.4 yıl olduğu görüldü. Yüzde üç hastanın COVID-19 aşısı/enfeksiyonu ile ilişkisi vardı.

Sonuç: Çalışmamız hem pediatrik hem de erişkin hastaları içermesi nedeniyle değerlidir. Ayrıca COVID-19 döneminde zona için bir yıllık demografik verileri sunmamız da literatüre katkı sağlamaktadır.

Anahtar kelimeler: Asiklovir, COVID-19, herpes zoster, nevralji.

INTRODUCTION

Herpes zoster infection (shingles) occurs due to reactivation of the varicella zoster virus (VZV) usually contracted during childhood. VZV can remain latent in the dorsal sensory or cranial nerve ganglia. It is known that impairment in the cellular immune response is determinative in the formation of this infection[1].

Diagnosis of herpes zoster is usually made upon clinical findings and is typically characterized by a dermatomal and unilateral vesicular rash and pain[1].However, this affliction may also present atypical clinical symptoms such as Zoster Sine Herpete (pain, burning, itching without skin rash), affecting non-adjacent dermatomes and bilateral shingles[2].

Herpes zoster causes health complications more serious than simple skin rash; some can cause disability, serious morbidity or even a fatal outcome. Secondary bacterial infections, motor or sensory nerve palsies, encephalitis, myelitis, cerebral arteritis, voiding disorders, Ramsey-Hunt syndrome, stroke, ocular complications and postherpetic neuralgia are some of the critical complications that may develop subsequent to herpes zoster infection[3].

Various dermatological diseases associated with COVID-19 infection have been reported in the literature, and shingles is one of these diseases. COVID-19 infection causes a serious decrease in monocytes, eosinophils, B and T lymphocytes and NK cells. The general weakening of the immune system thereafter possibly facilitates the formation of shingles, which is a latent infection[4].

Antiviral agents are used in the treatment of herpes zoster with the aim of preventing secondary complications and accelerating recovery time. Antivirals used systemically in the treatment of herpes zoster are valacyclovir, acyclovir, famciclovir, and brivudine. It has been reported that foscarnet and cidofovir are also effective. The patient's age, accompanying

systemic diseases, special conditions such as pregnancy/lactation, and immune condition are important in determining a treatment strategy. In addition, systemic corticosteroids may also be used in special cases such as Ramsey-Hunt and severe acute pain[5].

The aim of this study is to evaluate the demographic and clinical data collected from patients admitted to our tertiary referral medical center and diagnosed with herpes zoster during the COVID-19 pandemic period. The aim of our study was to evaluate the course of herpes infection triggered by immune deficiency during the COVID-19 pandemic period and to evaluate demographic and clinical data in order to compare this course with other immunodeficiency conditions. Prior research has focused on either pediatric cases or adult cases exclusively; no reports covering these two groups together have been found. The objective of this study is to obtain epidemiological data on the demographic and clinical characteristics of patients diagnosed with herpes zoster from the age of one year old.

METHOD

Ethics committee approval

Istanbul Kent University Ethics Committee approved this research project (Approval number:2021/02). The study was conducted in accordance with good clinical practices and the Declaration of Helsinki.

Data collection

The retrospective study data were obtained from our tertiary referral hospital (Basaksehir Cam and Sakura City Hospital). The study considers 661 patients admitted to the Dermatology Clinic or consulted from other clinics between October 2020 and October 2021. The common factor is that all patients in the study group were clinically diagnosed with herpes zoster.

Our study included patients aged between 1-90 years, who were first diagnosed or confirmed by the doctors of our dermatology clinic, and who had dermatomal or generalized umbilical vesicles (hemorrhagic or non-hemorrhagic) on the skin in addition to acute clinical symptoms such as pain, itching, and burning. In addition, herpes zoster with or without complications in the ICD-10 code was accepted as a mandatory criterion for inclusion in the study.

The age of the patients, the localization of the shingles lesions, the season and month at the time of shingles, comorbidities, hospitalization status, accompanying complications, association with COVID-19 vaccine/infection, predisposing factors, and prescribed systemic antiviral treatments were recorded.

The only exclusion criterion was defined as the lack of any required data.

RESULTS

SPSS 22.0 package program was used for data analysis. Frequency values and mean values of the patients' demographic characteristics were calculated.

Among 661 herpes zoster patients enrolled in the study, the age range was between 1 and 90; the mean age was 50.4±19.9 years; 50% were female and 50% male (Table I).

Table I: Demographic Data of Patients

			Frequency		*Percentage (%)*
Gender					
Female			333		50,4
Male			*328*		*49,6*
Total			*661*		*100,0*
Diseases experienced upto 6 months prior to the onset of shingles					
No			580		87,7
Yes			*81*		*12,3*
Total			*661*		*100,0*
	N	***Mean***	***Sd.***	***Min.***	***Max.***
Age	*661*	*50,44*	*19,91*	*1*	*90*

frequency and descriptive statistical analysis were applied

When the diseases (such as MI, malignancy, stroke, trauma) of the patients experienced up to 6 months prior to the onset of shingles were evaluated, it was observed that 88% of them did not have any disease (Table I).

It was determined that 17% of herpes zoster patients were admitted in January, 14% in October, 13% in August, 11% in September. When analyzed seasonally, it was observed that 32% were admitted in winter, 31% in autumn, 22% in summer and 15% in spring. Examination of the patients' involvement sites charts afflicted areas as 14% facial, 7% cervical, 42% thoracic, 23% lumbar, 8% sacral, 6% femoral, 2% tibial, 5% brachial involvement; 1% dissemination was observed. Mean recovery period until total cure was 67.8±91.1 days on average (Table II).

Table II: Period of Application of the Patients

Month of the year	*Frequency*	*Percent (%)*
January	*113*	17,1
February	*42*	6,4
March	*38*	5,7
April	*30*	4,5
May	*34*	5,1
June	*18*	2,7
July	*47*	7,1
August	*83*	12,6
September	*71*	10,7
October	*95*	14,4
November	*36*	5,4
December	*54*	8,2
Total	*661*	100,0
Season		
Spring	*102*	15,4
Summer	*148*	22,4
Autumn	*202*	30,6
Winter	*209*	31,6
Total	*661*	100,0

frequency analyses were applied

Complications were found in 62% of patients included in the study. When complications were examined, it was observed that 54% of the patients had postherpetic neuralgia, 11% had pruritus, 10% had hypopigmentation and 11% had scarring.

A history of an additional comorbidity was found in 79% of patients. It was observed that 50% of them had systemic diseases (chronic obstructive pulmonary disease (COPD), asthma, diabetes mellitus (DM), hypertension, osteoporosis, autoimmune diseases), and 34% had underlying psychogenic factors (mental stress, sorrow, death of a relative etc.) (Table III).

Table III: Evaluation of concomitant diseases

Accompanying Diseases		*No*	*Yes*
Infections (upper respiratory, urinary infections…)	*Frequency*	*582*	79
	Percentage (%)	*88,0*	12,0
Covid-19 (vaccine and/or infection)	*Frequency*	642	19
	Percentage (%)	97,1	2,9
Malignancy (hematologic+solid organ tumors…)	*Frequency*	*623*	38
	Percentage (%)	*94,3*	5,7
İmmunedeficiency (use of systemicsteroid, AIDS, chemotherapy/radiotherapy…)	*Frequency*	584	77
	Percentage (%)	88,4	11,6
Systemic Diseases (COPD, DM, autoimmune diseases…)	*Frequency*	332	329
	Percentage (%)	50,2	49,8
Pregnancy	*Frequency*	652	9
	Percentage (%)	98,6	1,4
Predisposing factors (obesity, chronic pruritus, allergy…)	*Frequency*	471	190
	Percentage (%)	71,3	28,7
Psychogenic Factors (stress, sorrow…)	*Frequency*	435	226
	Percentage (%)	65,8	34,2

frequency analyses were applied

Systemic antiviral drugs were given to 89% of patients: 53% had valacyclovir, 20% had brivudine, and 15% had acyclovir.

Data of hospitalized patients

It was observed that 10% of patients were hospitalized, and their mean age was 66.26±14.4 years (between 24 and 90 years). Fifty-two percent were female and 48% were male.

The involvement sites were as follows: 27% facial, 14% cervical, 35% thoracic, 23% lumbar, 9% sacral, 8% femoral, 2% tibial, 2% brachial. Complications were observed in 67% of patients. Considering the complications, 65% of patients had postherpetic neuralgia (PHN), 14% had hypopigmentation, 12% had scar, 8% had keratoconjunctivitis. Eighty percent of patients had additional underlying diseases: 55%

suffered systemic diseases (COPD, asthma, diabetes mellitus, hypertension, osteoporosis, autoimmune diseases) and 41% had psychogenic factors (mental stress, sorrow, death of a relative etc.).

Association with COVID -19 infection/vaccine

It was observed that 3% of the 661 herpes zoster patients had an association with COVID-19 vaccine/infection. The mean age was 48.05±23.05 years (between 8 and 85 years); 47% of the patients were female and 53% were male (Table IV). Considering the involvement sites, there were thoracic lesions in 47.4%, sacral lesions in 15.8%, facial lesions in 15.2%, femoral lesions in 10.5%, lumbar lesions in 5.3% and brachial lesions in 10.5% of the patients (Table V).

Table IV: Data on shingles and COVID -19 vaccine/infection

	Frequency			*Percentage (%)*	
Covid-19					
No			642		97,1
Yes			*19*		*2,9*
Total			*661*		*100,0*
Gender					
Female			9		47,4
Male			*10*		*52,6*
Total			*19*		*100,0*
	N	***Mean***	***Sd.***	***Min.***	***Max.***
Age	*19*	*48,05*	*23,05*	*8*	*85*

frequency and descriptive statistical analysis were applied

Table V: Involvement Sites of Herpes Zoster in COVID-19 Patients

Involvement Sites		*No*	*Yes*
Facial	*Frequency*	*16*	3
	Percentage (%)	*84,2*	15,2
Cervical	*Frequency*	19	0
	Percentage (%)	100,0	0,0
Thoracic	*Frequency*	*10*	9
	Percentage (%)	*52,6*	47,4
Lumbar	*Frequency*	18	1
	Percentage (%)	94,7	5,3
Sacral	*Frequency*	16	3
	Percentage (%)	84,2	15,8
Femoral	*Frequency*	17	2
	Percentage (%)	89,5	10,5
Tibial	*Frequency*	19	0
	Percentage (%)	100,0	0,0
Brachial	*Frequency*	17	2
	Percentage (%)	89,5	10,5
Disseminated	*Frequency*	19	0
	Percentage (%)	100,0	0,0
	Percentage (%)	100,0	0,0

frequency analyses were applied

DISCUSSION

Our study is a single center retrospective study and is unique because the patients who applied to the tertiary level dermatology outpatient clinic during the COVID-19 pandemic were evaluated. In addition, no study was found in the literature that evaluated both pediatric and adult age groups together.

The study by Rogers et al. revealed that herpes zoster mostly occurs over the age of 50; only 10% of reported cases are under 20 years of age[6]. In another epidemioclinical study, the most common age range in 525 herpes zoster patients was determined as 40-49 years[7].In our study, the mean age of the patients was 50.4 years. This situation was found to be compatible with a study conducted in the U.S.A. and other available data in the literature. In addition, the age of hospitalized patients and the preponderance of females were consistent with the literature[8]. In our study, it was a remarkable finding that the mean age of patients who had COVID-19 infection decreased slightly. We think that the introduction of psychogenic factors in the COVID-19 pandemic and the effect of quarantine conditions may be influential in this circumstance.

In our study, 53% of patients with COVID-19 infection were male. This may be related to the slight increase in the number of male patients with COVID-19 infection compared to females, and the more severe course of this infection in males[9,10]. Further molecular studies will clarify this issue.

Toyama et al. conducted the largest study with 48,388 herpes zoster patients. They reported that the disease peaked in August when considering the month of the year[11]. In our study, the incidence of the disease increased during the winter season and therefore differed from the aforementioned study. This difference

was attributed to the peak of the COVID-19 pandemic during winter months, the increase in quarantine measures and the increase in associated stress factor. Common sites of herpes zoster lesions were reported to be thoracic (55%), cranial (20%, most commonly trigeminal nerve involvement), lumbar region (15%) and sacral region (5%), respectively[12]. Our study identified involvement areas occurring at similar rates that make our data compatible with those reported in the literature. There was no statistical difference in terms of involvement in patients who had COVID-19 infection. However, in our study, when the involvement sites of COVID-19-positive zoster patients were examined, it was remarkable that the sacral involvement was higher (16% in patients with COVID-19, 9% in other patients).

Postherpetic neuralgia (PHN) is one of the most common complications related to herpes zoster infection. It causes both economic burden and morbidity due to its long duration. Studies show that the incidence of PHN is associated with increasing age and other risk factors, with a prevalence of 5-22%[13]. Another study revealed that PHN was observed in 34% of those with herpes zoster in the general population; however, this rate increased to 60-70% in patients aged 60 and over[1]. Besides, it has been reported that early antiviral therapy reduces this complication. Nonetheless, in our study, the prevalence of PHN was found to be 54%, although 89% of the patients was given systemic antivirals. This may be due to the fact that the initiation of antiviral therapy alone was the only determinant, but the time of onset was also important. In our study, the time elapsed between the initiation of systemic treatment and the onset of symptoms was not examined. In order to reveal the causality relationship more accurately, there is a need for studies comparing similar groups in terms of age, comorbidities and facilitating factors correlated to those patients' start date for pharmaceutical therapy.

In a review, hospitalization rate due to primary herpes zoster was found between 29% and 42%. It has been reported that hospitalization rates are also associated with advanced age[14]. In our study, the hospitalization rate for primary herpes lesion was found to be 10%, and the mean age was 66.26 years. The relatively low rate of hospitalization may be due to patient preferences, changes in hospitalization processes due to the COVID-19 pandemic, and lower rates of expected complications during the examination.

In their study, Donahue et al. reported that immunocompromised patients (neoplastic diseases, especially lymphoproliferative cancers; immunosuppressive drugs, organ transplantation and diabetes) were more frequently stricken with shingles compared to general population[15]. The relationship between herpes zoster and malignancies was discussed for the first time in the literature in the 1980s. When the cancers associated with herpes zoster were examined, it was reported that the closest relationship was with hematological malignancies; especially with the lymphoid series. In addition, the absolute risk of developing any cancer within 1 year after shingles has been stated as 0.7-1.8%. An increased risk of solid organ malignancies has also been observed in patients with herpes zoster[16]. In another study, the most common type of cancer accompanying shingles was reported as colorectal[17]. Yavaşoğlu et al. reported that 3 out of 10 cases were found to be accompanied by cancer[18]. In a case series of 132 patients, concomitant malignancy was found in 8 (6.1%) patients[19]. In our study, a concomitant malignancy was detected in 38 (5.7%) of 661 herpes zoster patients. In addition, conditions such as taking immunesuppressive drugs and HIV positivity were observed at a rate of 11.6%, the presence of infection at a rate of 12%, and

most importantly, COVID-19 infection and vaccine was observed at a rate of 2.9%. In this study, COVID-19 positivity was determined by polymerase chain reaction test result, and a causal relationship was established. In terms of COVID-19 infection, we believe that asymptomatic individuals can actually increase this rate even more.

One of the limitations of the study is that VZV vaccine status was not evaluated and the hemogram values were not correlated by examining cases associated with COVID-19. Examination of hemogram parameters will enable us to evaluate immune parameters such as lymphocytes and obtain numerical data between the state of the immune system and herpes zoster infection. Furthermore, the inability to determine whether the lesions of patients with shingles are precursors of any malignancy is another limitation.

In our retrospective archive-based study, the number of patients in a year, demographic characteristics, seasonal distributions, and clinical features of the disease were examined during the COVID-19 pandemic period. We attempted to reveal similarities and differences by comparing with other studies conducted in different countries.

The particular value of our study is its unique analysis of one-year data on herpes zoster infection during the immensely disruptive COVID-19 pandemic. A slight increase in male shingles patients and an increase in sacral involvement in COVID-19 positive herpes zoster patients were the most remarkable findings. We expect that hypotheses or molecular findings will gradually emerge over the years to explain these results. In addition, conditions where the immune system is suppressed such as viral infections, malnutrition and cancer play a triggering role. We think that our study will contribute to the literature in order to evaluate whether the COVID-19 pandemic is considered a predisposing factor for shingles in the future.

Ethics Committee Approval: Istanbul Kent University Ethics Committee approved this research project (Approval number:2021/02). The study was conducted in accordance with good clinical practices and the Declaration of Helsinki.

Conflict of Interest: The authors declared no conflicts of interest.

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