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Herpes Zoster in Children with Underlying Comorbidities: Evaluation of the 10-Year Retrospective Single Center Experience

Altta yatan Komorbiditeleri Olan Çocuklarda Herpes Zoster: 10 Yıllık Retrospektif Tek Merkez Deneyiminin Değerlendirilmesi

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Abstract

Aim: It was aimed to evaluate the complications and prognosis of pediatric patients diagnosed with Herpes zoster (HZ) with an underlying comorbidity.

Material and Method: Between 01.01.2011-01.01.2021 in our clinic; patients aged 0-18 years, with underlying comorbidities and diagnosed with HZ, who were followed up and treated, were evaluated retrospectively. A total of 45 patients were included in the study. Sociodemographic characteristics, clinical findings, treatments applied during hospitalization, complications developed during follow-up and prognosis were obtained from hospital file archive records.

Results: The mean age was 9.25±4.79 years, and 53.4% of patients were male. The most common symptom was rash, followed by pain and itching. Most commonly, 23 (51.1%) patients had thoracic dermatome involvement. Dissemination did not develop in any of the patients. 11.1% of the patients had chickenpox, 6.6% had Varicella vaccine, and 44.4% had no history of Varicella Zoster Virus transmission. Acute leukemia and having had a bone marrow transplant were the most common co-existing conditions. Median time between onset of symptoms and diagnosis was 3 (min-max=1-10) days. Median length of hospitalization was 7 (min-max=3-21) days, and the mean total treatment time was 9.33±3.58 days. It was determined that only four patients developed secondary skin infection, 44 patients were cured, and 1 patient died due to the primary disease.

Conclusion: While HZ is rare in healthy children, it can progress with serious complications in those with an underlying disease. To consider HZ in differential diagnosis of vesicles in immunocompromised patients, to start treatment with early diagnosis; It is of great importance in terms of complications and prognosis that may develop.

Keywords: Herpes zoster, child, underlying disease, immunocompromise, prognosis

Öz

Amaç: Altta yatan ek hastalığı olan Herpes zoster (HZ) tanısı almış çocuk hastaların komplikasyonlarının ve prognozlarının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Kliniğimizde 01.01.2011-01.01.2021 tarihleri arasında 0-18 yaş arası altta yatan ek hastalığı bulunan ve HZ tanısı konularak takip ve tedavi edilmiş hastalar retrospektif olarak değerlendirildi. Çalışmaya toplamda 45 hasta dahil edildi. Sosyodemografik özellikleri, klinik bulguları, hastane yatışları süresince uygulanan tedaviler ve takipte gelişen komplikasyonları ve prognozları dosya kayıtlarından elde edildi.

Bulgular: Ortalama yaş 9,25±4,79 yıl olup hastaların %53.4'ü erkek idi. En yaygın semptom döküntü iken bunu ağrı ve kaşıntı izlemekteydi. En sık olarak 23 (%51.1) hasta ile torakal dermatom tutulumu mevcuttu. Dört (%8.8) hastada birden fazla dermatom tutulumu vardı. Hastaların hiçbirinde disseminasyon gelişmedi. Hastaların %11,1'i suçiçeği geçirmiş, %6,6'sı suçiçeği aşısı olmuş, %44,4'ünün Varisella Zoster Virus enfeksiyonu geçirme öyküsü bilinmiyordu. Akut lösemi ve kemik iliği nakli olmuş olma en sık altta yatan ek durumlardandı. Semptomların başlama ve tanı koyma arasındaki ortanca süre 3 (min-max=1-10) gündü. Hastaların tümüne asiklovir tedavisi başlandı. Yatış ortanca süresi 7 (min-max=3-21) gün, toplam tedavi süresi ortalama 9,33±3,58 gündü. Sadece dört hastada sekonder cilt enfeksiyonu geliştiği, 44 hastanın şifa ile iyileştiği ve 1 hastanın primer hastalığı nedeniyle exitus olduğu saptandı.

Sonuç: HZ sağlıklı çocuklarda nadir iken alta yatan hastalığı olanlarda ciddi komplikasyonlarla seyredebilir. İmmünkompromize hastalarda veziküllerin ayırıcı tanısında HZ'yi düşünmek, erken tanı konularak tedavi başlamak; gelişebilecek komplikasyonlar ve prognoz açısından büyük öneme sahiptir.

Anahtar Kelimeler: Herpes zoster, çocuk, altta yatan hastalık, immünkompromize, prognoz

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INTRODUCTION

Herpes zoster (HZ), also known as shingles, is a viral infectious disease that occurs as a result of the reactivation of the latent Varicella Zoster Virus (VZV) in the sensory ganglia. It is characterized by a painful, vesicular rash, usually unilateral, limited to the dermatome.[1,2] Shingles is a disease seen in old age. It is extremely rare in healthy children. The incidence of HZ infection is 2.6/1000 per year in children with previous chickenpox.[3] Lesions are usually in thoracic and cervical dermatomes and the most common symptoms are pain and itching.[3]

Especially with T cell deficiency, HZ may progress more frequently and severely in cases of immunodeficiency such as Human Immunodeficiency Virus infection, malignancies such as leukemia or lymphoma, transplant recipients, primary immunodeficiency, and use of immunosuppressive drugs.[1,4-6] It can lead to serious complications such as postherpetic neuralgia, visceral dissemination, HZ ophthalmicus, HZ oticus, acute retinal necrosis, neurological (aseptic meningitis, encephalitis, myelitis, Guillain Barre Syndrome), secondary bacterial infection, and even death, especially in immunocompromised patients.[1,4,7-9] Early diagnosis and treatment in immunocompromised individuals determine the prognosis.

The aim of this study was to evaluate the demographic clinical features of pediatric patients diagnosed with HZ with an underlying disease, and to determine the complications and prognosis of the disease in these patients.

MATERIAL AND METHOD

Patients under the age of 18 with an underlying disease diagnosed with HZ, who were followed up in the Çukurova University Medical Faculty, in Department of Pediatric Infection Disease Clinic between 01.01.2011 and 01.01.2021, were included in the study. The files of the patients were reviewed retrospectively. The age, gender, complaint and duration of admission, underlying diseases, immunosuppressive drugs used, physical examination findings, laboratory findings, Varicella or vaccination status, duration of hospitalization, treatment and duration, complications and prognosis were recorded in the follow-up sheets. The diagnosis of HZ was made by physical and clinical examinations. Ethical approval of the study was obtained from the local ethics committee (No: 108, 12/02/2021). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical analysis

SPSS version 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) was used for statistical analysis. Categorical measurements were summarized as numbers and percentages, and continuous measurements as mean, deviation, and minimum-maximum.

RESULTS

In a 10-year period, 50 patients were diagnosed with HZ. Five healthy patients were excluded from the study. 45 patients with underlying disease were included in the study. 24 patients (53.4%) were male and 21 (46.6%) were female. The mean age was 9.25±4.79 years. Nine (20%) patients were immigrants. 11.1% of the patients had chickenpox, 6.6% had Varicella vaccine, 37.8% was Varicella IGG positive, and the history of VZV was unknown in 44.4%. The demographic characteristics of the patients are shown in **Table 1**.

Table 1. Demographic Characteristics of Patients with Herpes Zoster

		Mean±SD
Age (year)		9.25±4.79
Hospitalization period (day)		7.89±4.17
Treatment period (day)		9.33±3.58
		n (%)
Gender	Male	24 (53.4)
	Female	21 (46.6)
Ethnicity	Turkish Republic citizen	36 (80)
	Syria	9 (20)
Encountering with Varicella	Chickenpox	5 (11.1)
	Chickenpox vaccinated	3 (6.6)
	Varicella IGG positivity	17 (37.8)
	Unknown	20 (44.4)
Dermatome involvement	Thoracic	23 (51.1)
	Cervical	6 (13.3)
	Trigeminal	5 (11.1)
	Lumbar	5 (11.1)
	Sacral	2 (4.4)
	Lumbar + Sacral	2 (4.4)
	Thoracic + Cervical	1 (2.2)
	Cervical+ Trigeminal	1 (2.2)

The most common involvement was thoracic dermatome in 23 (51.1%) patients. Six (13.3%) patients had cervical, five (11.1%) trigeminal, five (11.1%) lumbar, and two (4.4%) patients had sacral involvement. Four (8.8%) patients had more than one dermatome involvement. Two (4.4%) patients had lumbar and sacral involvement, one (2.2%) patient had thoracic and cervical involvement, and one (2.2%) patient had cervical and trigeminal involvement. None of the patients had facial nerve and generalized involvement. No involvement was detected in the eye examination of the patient with trigeminal involvement.

The most common symptom was pain and itching after the rash. 21 (46.6%) patients had only rash, 12 (26.6%) had pain, four (8.8%) had itching, four (8.8%) had pain and itching, three patients (6.6%) had fever, and one (2.2%) patient had pain and fever. Median time between onset of symptoms and diagnosis was 3 (min-max=1-10) days.

The most common underlying diseases were acute leukemia and bone marrow transplantation (**Table 2**). 26 of the patients were receiving active chemotherapy, three patients were

using high-dose steroids, and six patients were using other immunosuppressive drugs. Two patients were receiving monthly IVIG therapy. 10 patients were not receiving any treatment.

Table 2. Underlying Diseases of the Patients

	n (%)
Acute leukemia	17 (37.7)
Bone marrow transplant	9 (20)
Lymphoma	3 (6.6)
Medulloblastoma	3 (6.6)
Solid organ transplant	2 (4.4)
Hemophagocytosis	2 (4.4)
Immunodeficiency	2 (4.4)
Chronic myeloid leukemia	1 (2.2)
Angiosarcoma	1 (2.2)
Histiocytosis	1 (2.2)
Malignant mesenchymal tumor	1 (2.2)
Uveitis *	1 (2.2)
Metabolic disease	1 (2.2)
Nephrotic syndrome	1 (2.2)

*Biological agent use

Acyclovir treatment was started in all patients. Intravenous acyclovir treatment at a dose of 10 mg/kg/dose three times a day or oral acyclovir 80 mg/kg four times a day was administered. The median hospital stay was seven (min-max=3-21) days, and the mean total treatment time was 9.33±3.58 days.

Secondary skin infection developed in only four (8.8%) patients. It was determined that 44 patients recovered with healing and one patient died due to the primary disease.

DISCUSSION

The Centers for Disease Control and Prevention (CDC) estimates that about 30% of people in the United States will have HZ in their lifetime.[10] HZ can occur at any time after people have had chickenpox infection or have been vaccinated. It is rare in healthy children, however the occurrence of HZ does not always mean that there is an underlying immunodeficiency or malignancy.[11] Early diagnosis and treatment in HZ infection are of great importance in terms of preventing complications and prognosis.

The most common symptoms of the disease are pain and pruritus associated with a unilateral vesicular rash, typically involving a single dermatome. These symptoms interfere with quality of life and may impair functionality.[2] Studies have reported that the most common symptoms in healthy children are pain, followed by itching and fever.[12,13] In a study, it was reported that fever, pain, and general symptoms were less common in immunocompromised patients compared to healthy children, and itching was more common.[14]

In our study, the most common symptoms were pain, followed by itching and fever, and 4.4% of the patients did not have any complaints and were discovered by chance. HZ should be considered in the differential diagnosis of vesicle in immunocompromised patients and patients with underlying disease, and it should also be considered that it may be asymptomatic. Even if there are no symptoms, especially in immunosuppressive patients, the importance of performing a detailed physical examination has emerged once again.

The most common dermatome involvement is seen in the thoracic region. Different results in terms of localization of the lesion have been reported between immunocompromised and immunocompetent patients. It has been reported in studies that thoracic and trigeminal dermatomes are the most frequently involved, respectively, and lumbar-sacral dermatome is more common in immunocompromised patients.[7,15] Kuchar et al.[14] reported that thoracic and cranial-cervical dermatome involvement was the most common, but there was no difference in terms of localization between immunocompromised and healthy patients. It has been reported that dissemination is more common in immunocompromised patients.[14,15] All of the patients in our study were immunosuppressive patients with an underlying disease, and we found thoracic, cervical, trigeminal, and dermatome involvement, respectively (51.1%, 13.3%, 11.1%). We did not have any patients with disseminated involvement, but four (8.8%) patients had involvement in two different dermatomes. More than one dermatome has not been reported in studies conducted in healthy children in the literature.[12,13] These results support the conclusion that more than one dermatome involvement and the risk of dissemination are higher in immunocompromised patients. Consistent with the literature in terms of gender, it was found to be higher in males.[7,8,12,15] However, there are also studies reporting that it is more dominant in females.[16] In general, the incidence is lower in children aged 0-5 years compared to adolescents.[17] In the literature, they found the incidence to be high between the ages of 7-14 years.[4,8,18,19] The median age in our patient group was 10.08 years. The age of onset of shingles is similar between immunocompromised and immunocompetent patients.[4,15]

The most common complication of HZ is post-herpetic neuralgia. Other complications include bacterial superinfection of the eye, neurological system, and skin. Immunocompromised patients are at risk of more frequent episodes of HZ and/or serious complications associated with VZV. Serious complications include cutaneous spread and visceral involvement.[2] Grote et al.[7] reported that the most common skin infections were ophthalmic zoster and meningoencephalitis as complications, and that no complications other than disseminated HZ were statistically significantly more common in immunocompromised children. Takayama et al.[15] reported complications of dissemination, meningitis, and facial nerve palsy, and they found no difference between the two groups. Kuchar et al.[14] also found no difference between the two groups in terms

of complications. Kanamori et al.[8] observed that the most common complication was secondary skin infection, and facial paralysis, uveitis/keratitis, and acute retinal necrosis were more serious complications, and they reported complications to be more frequent in immunocompromised patients. In our study, secondary skin infection was seen in only four patients. With these results, it should be emphasized that the disease is not always a mild course in healthy children, and it can be seen with serious complications such as in patients with an underlying disease. It has been reported that the incidence of HZ is high in immunocompromised patients, complications are more common, and the hospitalization period is long.[6,20-22] However, Grote et al.[7] reported that 41% of the 244 HZ patients who were hospitalized and followed up had an underlying disease (32% immunosuppressed and the majority of them were hemato-oncological diseases) and the average hospitalization period was 7 (min-max=5-10) days. All of our patients were hospitalized and 37.7% had leukemia. The average length of hospital stay was 7 (min-max=3-21) days. The duration of hospitalization and treatment differed from patient to patient.

In order to heal HZ lesions faster, to prevent the development of new lesions, to reduce the risk of transmission, and to reduce the severity and duration of pain associated with acute neuritis, it is recommended to start treatment in the first 72 hours after the onset of symptoms.[23,24] In immunocompromised patients, treatment should be initiated even if they apply to the hospital later. Recognition of symptoms and initiation of early treatment are of great importance, especially in cancer patients, in children with cancer since HZ can cause serious complications such as herpetic neuralgia, dissemination, acute or progressive outer retinal necrosis and even death.[4]

Acyclovir has been shown to be effective in the treatment of HZ in healthy and immunocompromised patients. We started acyclovir intravenously in all of our patients because they had an underlying disease independent of the duration of the symptoms. Therefore, we did not see any serious complications. Although the duration of treatment is 7 days on average, it can be continued until two days after the new lesion has stopped.[2,25] In our study, the mean duration of acyclovir treatment was found to be 7 days. However, we had a patient who received treatment for 21 days depending on his clinical condition. We think that it would be an appropriate approach to decide the duration of treatment, especially in immunocompromised patients, according to the clinical situation and to evaluate it on a patient basis.

The most important risk factor for the development of HZ has been reported to be intrauterine or chickenpox in the first years of life.[26] The main reasons for the development of HZ in pediatric patients are, the immature immune system and low cellular response, and primary infection in the first year of life.[26] Although it has been suggested that Varicella vaccine may increase the risk of HZ in immunocompromised patients, several studies have reported that Varicella vaccine reduces the incidence of HZ.[27,28] However, the effectiveness of vaccination in preventing complications is unknown. In our study, 44.4% of the patients did not have any information or evidence of previous vaccination or chickenpox. Only five patients had a history of chickenpox, and three patients had a history of vaccination. In 17 of the patients, Varicella IGG was positive, and we could not reach sufficient information whether these antibodies were from vaccinated or not. In our study, HZ was evaluated only in patients with underlying disease. Therefore, the data are limited. Healthy children were excluded from the study due to the very small number of children. More multicenter studies are needed to compare the two groups in terms of frequency and prognostic complications.

CONCLUSION

HZ can be seen in healthy or immunocompromised pediatric patients. It may be more frequent and at risk for complications in immunosuppressive patients with underlying disease. Considering HZ in the differential diagnosis of vesicle, especially in patients with underlying disease and immunocompromised, is of great importance in terms of early diagnosis, initiation of treatment, complications, and prognosis.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval was obtained from Çukurova University Non-Interventional Clinical Research Ethics Committee (Date: 12/02/2021, Number of Meeting/ Decision No:108/4).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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