ORIGINAL ARTICLE ÖZGÜN ARAŞTIRMA

Herpes Zoster in Children; Should the Varicella Vaccine be Administered as a Single Dose or a Double Dose?

Çocuklarda Herpes Zoster; Suçiçeği Aşısı Tek Doz mu Yoksa Çift Doz mu Uygulanmalı?

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Abstract

Introduction: In this study, we aimed to evaluate the clinical and epidemiological characteristics of children followed up with the diagnosis of herpes zoster, together with the data of our country.

Materials and Methods: Patients who were followed up with the diagnosis of "Herpes Zoster" in the Pediatric Infectious Diseases Clinic of Kayseri Training and Research Hospital between 2016-18 were analysed retrospectively.

Results: Twenty (69%) of 29 patients included in the study were female. The mean age of the patients, whose ages ranged from 2 to 16 years, was 8.86±0.6 years. Twenty (69%) of the patients had varicella infection and 6 (20.7%) had a history of single-dose varicella vaccination. The mean age of those who had varicella vaccine was 4.33±0.5, and those who had the varicella infection were 9.9±0.6 years. Four of the patients (13.8%) presented with only rash. Along with the rash, 25 patients (85.8%) had pruritus and 14 (48.3%) described pain. Thoracic dermatomes were most frequently involved with 69%, followed by cervical (17.3%), lumbar (10.3%) and trigeminal (3.4%) dermatomes, respectively. The patients had no known chronic disease, immunodeficiency (primary or secondary) or history of surgical intervention.

Conclusion: This study, emphasizes that varicella vaccination can change the epidemiology of HZ in healthy children, causing it to be seen at an earlier age, and emphasizes the importance of two-dose vaccination.

Keywords
Herpes zoster, child, vaccination

Anahtar kelimeler
Herpes zoster, çocuk, aşılama

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Öz

Giriş: Bu çalışmada, herpes zoster tanısı ile takip edilen çocukların klinik ve epidemiyolojik özelliklerini ülkemiz verileri ile birlikte değerlendirmeyi amaçladık.

Gereç ve Yöntem: Kayseri Eğitim ve Araştırma Hastanesi, Çocuk Enfeksiyon Hastalıkları Kliniği'nde 2016-18 yılları arasında "Herpes Zoster" tanısı ile takip edilen hastalar retrospektif olarak incelendi.

Bulgular: Çalışmaya alınan 29 hastanın 20'si (%69) kızdı. Yaşları 2 ile 16 arasında değişen hastaların yaş ortalaması 8,86±0,6 yıldı. Hastaların 20'sinde (%69) suçiçeği geçirme, 6'sında (%20,7) ise tek doz suçiçeği aşılaması öyküsü vardı. Suçiçeği aşısı olanların ortalama yaşı 4,33±0,5, enfeksiyonu geçirenlerin ise 9,9±0,6 idi. Hastaların 4'ünün (%13,8) başvuru yakınması sadece döküntüydü, 25'inde (%85,8) kaşıntı, 14'ünde de (%48,3) ağrı döküntüye eşlik ediyordu. Torakal dermatomlar en sık (%69) tutulurken, bunu sırasıyla servikal (%17,3),

lomber (%10,3) ve trigeminal (%3,4) dermatomlar izledi. Hastaların bilinen kronik hastalık, immün yetmezlik (primer veya sekonder) veya cerrahi girişim öyküsü yoktu.
Sonuç: Bu çalışma, suçiçeği aşılamasının sağlıklı çocuklarda HZ'nin epidemiyolojisini değiştirerek daha erken yaşlarda görülmesine neden olabileceği ve iki doz aşılamanın önemini vurgulamaktadır.

Introduction

Herpes zoster (HZ) is caused by reactivation of varicella zoster virus (VZV), which is latently found in the dorsal root ganglia of sensory nerves. Latent infection is controlled by VZV-specific cellular immunity. It usually develops with reactivation of latent VZV as a result of suppression of cellular immunity against VZV due to reasons such as immunodeficiency (1,2). However, HZ in childhood can be seen in healthy children or children with underlying immunodeficiency. Therefore, the presence of HZ in a young child does not always imply the presence of an underlying immunodeficiency or malignancy (3). Although it is predominantly seen in the adult population, the incidence increases in children who have had varicella in utero or in the first 1-2 years of life (1,3,4). Children who have an intrauterine infection are in 18% higher risk of HZ in the first few years of life (1). The incidence in children under the age of fourteen is 0.45 cases per 1000 people per year. When all age groups are taken into account, it varies between 1.2-3.4 cases per 1000 people per year, and increases to 3.9-11.8 per 1000 people over 65 years of age (3). Recently, there has been a trend towards an increase in HZ cases in childhood. Since the VZV vaccine is a live attenuated vaccine, there is a risk of HZ in vaccinated children, which may be one of the reasons for the increase in the number of cases (4). However, there is controversy over whether vaccination results in an increased incidence of HZ (5). Because the risk in children with a history of varicella is much higher than in vaccinated children (6). Therefore, considering the lower reactivation rate of the vaccine strain in the long term, the incidence of HZ is expected to decrease (7). However, vaccination may reduce the opportunities for VZV immunity due to intermittent native varicella exposure, resulting in an increased incidence of HZ in older adults. Because intermittent exposure to wild-type virus is assumed to provide adequate support to the immune system to keep VZV-specific cellular immunity above a critical threshold and to prevent VZV reactivation (5,8). In addition, it should be kept in mind that the causative agent may not always be a vaccine type virus in HZ that develops after vaccination. Wild-type virus has also been reported to cause HZ in vaccinated healthy children (6). It typically presents as a rash characterized by grouped vesicular skin lesions that are unilateral and dispersed into 1-3 sensory dermatomes, often accompanied by localized pain and/or pruritus on the affected area (1,2,4). Rash in vaccinated children can be severe and occur in the dermatome where the vaccine was injected or at a remote location (9).

In this study, we aimed to evaluate the clinical and epidemiological characteristics of children followed up with the diagnosis of herpes zoster, with the data of our country.

Materials and Methods

The data of the patients who were followed up with the diagnosis of "Herpes Zoster" in the Pediatric Infectious Diseases Clinic of Kayseri Training and Research Hospital between October 2016 and December 2018 were analysed retrospectively through the "Hospital Information Management System". Ethics committee approval dated 11.12.2019 and numbered 2019/20-17 was obtained from the Çanakkale Onsekiz Mart University Ethics Committee for our study. Information about the demographic data of the patients, their complaints on admission, physical examination findings (such as an involved dermatome), varicella infection or its vaccination history, presence of underlying disease, laboratory parameters, the season in which the disease occurred, and treatment results were recorded.

Statistical Analysis

Statistical Package for the Social Sciences program (SPSS, version 23.0, IBM Company) was used for statistical analysis of the data. Descriptive statistics such as mean ± standard deviation (SD) or continuous variables and frequency (n) and percentage (%) for categorical variables were used to summarize participant baseline characteristics.

Results

Twenty (69%) of 29 patients included in the study with the diagnosis of herpes zoster were female. The mean age of the patients, whose ages ranged from 2 to 16 years, was 8.86±0.6 years. Twenty (69%) of the patients had varicella infection and 6 (20.7%) had a history of single-dose varicella vaccination. Three patients were not vaccinated and their infection history was unknown. The mean age of those who had varicella vaccine was 4.33±0.5, and those who had the varicella infection were 9.9±0.6 years (Table 1). Four of the patients (13.8%) presented with only rash. Along with the rash, 25 patients (85.8%) had pruritus and 14 (48.3%) pain. The median time from the onset of symptoms to admission to the outpatient clinic was 3 (1-10 days) days. Thoracic dermatomes were most frequently involved with 69%, followed by cervical (17.3%), lumbar (10.3%) and trigeminal (3.4%) dermatomes, respectively (Table 2). The patients had no known chronic disease, immunodeficiency (primary or secondary) or history of surgical intervention. In addition, the vaccinated patients had no known varicella contact and no history of post-vaccination rash. When evaluated according to the season of admission, the patients presented most frequently in autumn with 44.8%, followed by spring (24.2%), winter (20.7%) and summer (10.3%), respectively.

Table 1. Age, gender, presenting complaint and seasonal distribution of patients according to varicella vaccination and infection history

Variable	Varicella	
	Infection (n=20) [n (%), mean ± SD]	Vaccination (n=6) [n (%), mean ± SD]
Age	9.9±0.6	4.33±0.5
Gender		
Female	13 (44.8%)	5 (17.2%)
Male	7 (24.1%)	1 (3.4%)
Symptom		
Rash	2 (6.9%)	1 (3.4%)
Rash and pruritus	7 (24.1%)	3 (10.3%)
Rash, pruritus and pain	11 (38%)	2 (6.9%)
Dermatome		
Thoracic	14 (48.3%)	3 (10.3%)
Cervikal	2 (6.9%)	3 (10.3%)
Lumbar	3 (10.3%)	-
Trigeminal	1 (3.4%)	-

*SD: Standard deviation

In the laboratory evaluation of the patients, the mean (± SD) total leukocyte count was 8.430±440/mm^3, hemoglobin was 13.2±0.1 gr/dL, platelet count was 292.722±8.660/mm^3, and C-reactive protein was 5.3±0.4 mg/dL. There were no special features in the immunological evaluation (serum immunoglobulin levels, lymphocyte subgroups) of 3 (10.3%) patients with recurrent "Herpes Zoster" history. Acyclovir treatment was started in all patients at the outpatient clinic admission. No treatment-related side effects were observed in the patients and no complications developed.

Discussion

Although well described in adults, HZ has not been extensively studied in the healthy pediatric population (10). Although varicella infection is common in childhood, HZ rarely occurs in childhood. Most childhood patients are over 5 years old, but the incidence is increasing in young children who had varicella in utero or before 2 years of age (1,11). The inclusion of the varicella vaccine in national immunization programmes around the world has reduced varicella infection (12). Since 2013 (those born after January 2012) in Turkey, varicella vaccine has been included in routine childhood vaccination programme as a single dose administration to 12-month-old children (13). Widespread use of the vaccine may reduce the circulating virus, leading to a decrease in cellular immunity in adults in later years, and thus undesirable consequences may cause such as an increased incidence of HZ. However, the incidence of HZ is expected to decrease, as vaccinated individuals in the long term are less likely to develop HZ compared to naturally infected individuals (7, 12). In our study, the number of patients who had varicella vaccine was small, but the mean age of HZ in these patients was quite low compared to the population with the infection. In studies in which HZ cases were reported from our country in general, the mean age ranged from 5.9 to 13 years. There was no significant difference in mean age in the pre- and post-vaccination period in these studies, but most of the studies did not have vaccinated HZ patients (11,14-23) (Table 3). Among these studies, Gündoğdu et al.

Table 2. Gender, mean age, pain complaint and duration of symptoms by affected dermatomes					
Dermatome	Gender (n, %)		Age (mean ± SD)	Pain (n, %)	Symptom duration (median, day)
	Female	Male			
Thoracic	17 (58.6%)	3 (10.3%)	9.9±0.7	9 (31%)	4
Cervical	2 (6.9%)	3 (10.3%)	6.4±1.7	2 (6.9%)	2
Lumbar	-	3 (10.3%)	6.3±1.7	2 (6.9%)	3
Trigeminal	1 (3.4%)	-	8	1 (3.4%)	3
Total	20 (69%)	9 (31%)	8.86±0.6	14 (48.3%)	3
*SD: Standard deviation					

Table 3. Patient characteristics in our study and studies published in Turkey											
Study	Study year	Number of cases (n)	Female gender (%)	Mean age (year)	Infection (%)	Vaccination (%)	Pruritus (%)	Pain (%)	Most common dermatoma	Concomitant disease* (n)	Complication (n)
Çölgeçen et al. (14)	2009-11	24	58.3	10.6	79.2	-	54.2	-	Thoracic (66.6%)	-	-
Şen et al. (15)	2010-11	16	56.2	7.3	50	6.2	6.2	25	Thoracic (37.5%)	SID (6)	Keratitis, secondary infection
Topkarcı et al. (16)	2011	14	28.5	8	92.8	-	42.8	35.7	Thoracic (64.2%)	-	-
Özuğuz et al. (17)	2011-13	12	33.3	8	50	16.6	33.3	8.3	Thoracic (58.3%)	-	-
Güven et al. (18)	2012-13	24	33.3	13	33.3	-	-	87.5	Thoracic (66.6%)	-	-
Tepe et al. (19)	2014	31	38.7	9.12	61.3	-	48.4	38.7	Thoracic (64.5%)	-	Hyperpigmentation, scar
Karagün (20)	2014-15	48	46	5.9	41.6	-	81.2	20.8	Lumbosacral (35.4%)	NS (1)	Ramsay-Hunt syndrome
Özçelik (21)	2014-16	55	50.9	10.16	58.1	1.8	16.3	16.3	Thoracic (52.7%)	DM (2)	Secondary infection
Aktaş et al. (11)	2012-18	60	38.3	8	76.7	5	80	63.3	Thoracic (36.7%)	-	-
Gündoğdu et al. (22)	2017-18	69	42	10.57	59.4	18	-	36.2	Thoracic (42%)	-	-
Öztürk et al. (23)	2017-18	21	42.9	10.1	71.4	-	-	-	Thoracic (66.6%)	ALL (2)	-
Our study	2016-18	29	69	8.86	69	20.7	85.8	48.3	Thoracic (69%)	-	-
*SID: Secondary immunodeficiency, NS: Nephrotic syndrome, DM: Diabetes mellitus, ALL: Acute lymphoblastic leukemia											

(22) evaluated 69 patients with a mean age of 10.5, and the mean age (4.9) of 13 (18%) patients with a history of varicella vaccine was similar to our study. Soysal et al. (12) evaluated 2049 patients (child and adult) with VZV-related disease between 2011-19 and reported that there was no difference in the incidence of HZ in children under 5 years of age between the pre- and post-vaccination periods. But similar to our observation, in this study, which 63 pediatric patients with HZ were evaluated, the number of cases younger than 5 years old was 6 in 2011-15, whereas it was 17 between 2016-19. There was no difference between these years in the group between the ages of 6-17. Again, Inan Yuksel et al. (24) evaluated a total of 190 patients with HZ, 119 of whom were vaccinated, and reported that the number of vaccinated cases <2 years and <5 years old was higher. Based on these studies, it can be said that the epidemiology of HZ in our country has changed after the single dose vaccination started to be used on a national scale in 2013, and healthy young children are now frequently affected. Rafferty et al. (25) from Canada reported that after the vaccination program was implemented, 50% of HZ occurred in children younger than 5 years old, and the rates in children who received two doses of vaccine were 41% lower than those who received a single dose of vaccine. Again, in this study, the risk of HZ with two doses of vaccine was 48% lower in children aged 1-4 years compared to a single dose vaccination. Similarly, Weinmann et al. (26) reported that the incidence of HZ in children who received 2 doses of varicella vaccine was lower than those who received 1 dose. Therefore, it is inevitable that HZ will emerge as an important cause of morbidity, especially in children <5 years old, in the near future in our country, where single-dose vaccination continues on a national scale. Wolfson et al. (27) reported that adding a second varicella vaccine at 18 months of age to the national immunization programme in Turkey is also cost-effective. So, we think that national administration of two doses of vaccine, which is among the recommendations of the Pediatric Infectious Diseases and Immunization Society (13), is important in terms of protecting the population under 5 years old from HZ. As a secondary outcome, it is also crucial to ensure the safety of immunocompromised children, who are at high risk for complications related to HZ for which vaccination is not possible (25).

Our study has limitations such as being conducted from a single centre, having a low population, and missing some data due to the nature of retrospective studies.

Conclusion

This study shows that although varicella vaccine reduces the incidence of infection and therefore HZ in healthy children, it may cause HZ to be seen at an earlier age. In addition, it emphasizes that switching to two doses instead of a single dose vaccination, which is still applied in our country, may reduce the frequency of HZ seen at early ages.

Ethics

Ethics Committee Approval: Ethical approval was received for this study from the local ethics committee of Çanakkale Onsekiz Mart University Faculty of Medicine (approval number: 2011-KAEK-27/2019-E.1900172605, date: 11.12.2019).

Conflict of Interest: No conflict of interest was declared by the authors.

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References

1. Gershon AA. Varicella-Zoster Virus. In: Cherry JD, Harrison GJ, Kaplan SL, Steimnbach WJ, Hotez BJ (eds). Feigin and Cherry's Textbook of Pediatric Infectious Diseases. 8th edition. Elseiver; 2019. p.1476-88.
2. American Academy of Pediatrics. Varicella-Zoster Virus Infections. In: Red Book, Kimberlin DW, Brady MT, Jackson MA, Long SS (eds). Red Book: Report of the Committe on İnfectious Diseases. 32nd ed. 2021;831-43.
3. Katakam BK, Kiran G, Kumar U. A prospective study of herpes zoster in children. Indian J Dermatol 2016;61:534-9.
4. Mitra B, Chopra A, Talukdar K, Saraswat N, Mitra D, Das J. A clinico-epidemiological study of childhood herpes zoster. Indian Dermatol Online J 2018;9:383-8.
5. Goldman GS. Insights on the impact of external and internal boosting on varicella-zoster virus reactivation based on evidence from the first decade of the United States universal varicella vaccination program. Cureus 2021;13:e16963.
6. Leung AK, Robson WL, Leong AG. Herpes zoster in childhood. J Pediatr Health Care 2006;20:300-3.
7. Akpo EIH, Cristeau O, Hunjan M, Casabona G. Epidemiological ımpact and cost-effectiveness of varicella vaccination strategies in the United Kingdom. Clin Infect Dis 2021;73:e3617-26.
8. Wutzler P, Casabona G, Cnops J, Akpo EIH, Safadi MAP. Herpes zoster in the context of varicella vaccination - An equation with several variables. Vaccine 2018;36:7072-82.

9. Moodley A, Swanson J, Grose C, Bonthius DJ. Severe herpes zoster following varicella vaccination in immunocompetent young children. J Child Neurol 2019:34;184-8.
10. Stein M, Cohen R, Bromberg M, Tasher D, Shohat T, Somekh E. Herpes zoster in a partially vaccinated pediatric population in central Israel. Pediatr Infect Dis J 2012;31:906-9.
11. Aktaş H, Erdal SA, Güvenç U. Herpes Zoster in children: Evaluation of the sixty cases. Dermatologic therapy 2019;32:e13087.
12. Soysal A, Gönüllü E, Yıldız I, Karaböcüoğlu M. Incidence of varicella and herpes zoster after inclusion of varicella vaccine in national immunization schedule in Turkey: time trend study. Hum Vaccin Immunother 2021;17:731-7.
13. Arısoy ES, Çiftçi E, Hacımustafaoğlu M, Kara A, Kurugöl Z, Somer A, et al. Vaccination in previously-healthy children: practice recommendations on vaccines ıncluded and not ıncluded in the national ımmunization schedule of the republic of Turkey - 2020. J Pediatr Inf 2020;14:180-93.
14. Çölgeçen E, Küçük Ö, Balci M. Clinical features of herpes zoster infections in childhood. Turkderm 2012;46:26-8.
15. Şen S, Bayram N, Bal Şahbudak Z, Yıldız KB, Helvacı M, Vardar F. Herpes zoster experience in two pediatric infection clinics. Turk Arch Ped 2013;48:40-3.
16. Topkarcı Z, Erdoğan B, Erkum T, Yilmaz M. Herpes zoster infection in healthy children. Medical Journal of Bakırköy 2012;8:178-81.
17. Özuğuz P, Kaçar SD, Polat S, Karaca S, Kundak A. Childhood zona zoster infection: 12 case reports. Abant Med J 2014;3:253-6.
18. Güven M, Bozkurt EÇ. Herpes zoster infection in childhood: an evaluation of 24 cases. Turkish J Pediatr Dis 2017;11:233-8.
19. Tepe B, Bucak IH, Almış H. Herpes zoster in healthy children: a retrospective study. Turk J Dermatol 2016;10:65-8.
20. Karagün E. Childhood herpes zoster infection: a retrospective study. Turk J Dermatol 2019;13:20-4.
21. Özçelik S. Herpes zoster in children: a retrospective study of 55 cases. Uludağ Üniversitesi Tıp Fakültesi Dergisi 2020;46:59-63.
22. Gündoğdu M, Erden N, Karagun E, Acıpayam AŞF, Vural S. Annual pattern and clinical characteristics of herpes zoster in immunocompetent children in a rural area. Dermatol Ther 2021;34:e14570.
23. Öztürk M, İsa AN, Aksoy M. Herpes zoster infection in childhood: prospective evaluation of 21 cases. Journal of Harran University Medical Faculty 2019;16:33-6.
24. Inan Yuksel E, Kara Polat A, Gore Karaali M, Koku Aksu AE, Gurel MS. Effect of the varicella vaccination ımplementation on the development of herpes zoster in children and adolescents. Dermatol Ther 2021;34:e14995.
25. Rafferty E, Reifferscheid L, Russell ML, Booth S, Svenson LW, MacDonald SE. The impact of varicella vaccination on paediatric herpes zoster epidemiology: a Canadian population-based retrospective cohort study. Eur J Clin Microbiol Infect Dis 2021;40:2363-70.
26. Weinmann S, Naleway AL, Koppolu P, Baxter R, Belongia EA, Hambidge SJ, et al. Incidence of herpes zoster among children: 2003-2014. Pediatrics 2019;144:e20182917.
27. Wolfson LJ, Daniels VJ, Pillsbury M, Kurugöl Z, Yardimci C, Kyle J, et al. Cost-effectiveness analysis of universal varicella vaccination in Turkey using a dynamic transmission model. PLoS One 2019;14:e0220921.