The Time of the Primary Varicella Zoster Virus Infection in Previously Healthy Children with Herpes Zoster: Is It Important?

Running title: Time of the Primary Varicella Zoster Virus Infection and Herpes Zoster

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ABSTRACT

Introduction: Herpes zoster (HZ) is unusual in children. Previous studies reported that HZ is more common among immunocompromised children. But, this disease can be seen in healthy children. Exposure to varicella zoster virus (VZV) in the early stages of life could be an important determinant for HZ development. In here, 17 healthy children who developed HZ were evaluated. In particular, the age at onset of HZ and the time interval between primary infection and HZ were interpreted in children who had been varicella within the first year of life and who had been varicella after the first year of life.

Material and Methods: In this retrospective study, we evaluated 19 children who was diagnosed with HZ admitted to xxxxxxxxxx, Departments of Pediatric Infectious Diseases, between July 2012 and June 2013. Among these children who had immunsupression such as immunodeficiency, malignancy and other immunodeficiency states were excluded the study.

Results: We evaluated 19 children who had diagnosed HZ. Two children with HZ were excluded from the study due to immunsupressive states. As a result, we evaluated 17 healthy children with HZ in this study. The median age at presentation was 9 years. Eight of them had been varicella within the first year of life. In only one patient exposure to VZV was in utero (32nd weeks of gestation). The most commonly involvement was thoracic dermatome (n=9, 52.9%). The median age at onset of HZ was significantly lower in children who had been varicella within the first year of life than children who had been varicella after the first year of life (7.5 years, 13.2 years, respectively, p=0.001). Also, the time interval between primary infection and HZ was significantly lower in children who had been varicella within the first year (80 months, 131 months, respectively, p=0.003).

Conclusions: The early time of the primary VZV infection is the determinant risk factor for herpes zoster in healthy children. Additionally, early exposure to VZV may be relevant to early presentation of HZ and shorter time interval between primary VZV infection and HZ.

Key words: Herpes zoster, healthy, child.

Öncesinde Sağlıklı Herpes Zosterli Çocuklarda Primer Varicella Zoster Virus Enfeksiyonu Zamanı: Önemli Mi?

Kısa Başlık: Primer Varicella Zoster Virus Enfeksiyonu Zamanı ve Herpes Zoster"

ÖZET

Giriş: Herpes zoster (HZ), çocuklarda ender görülmektedir. Yapılmış çalışmalarda, immunesupressif çocuklarda daha sık görüldüğü belirtilmiştir. Ancak, sağlıklı çocuklarda da görülebilmektedir. Yaşamın erken evrelerinde varisella zoster virüsa (VZV) maruz kalmak HZ gelişiminde önemli bir belirteç olabilir. Burada, HZ gelişen 17 sağlıklı çocuk değerlendirildi. Özellikle HZ başlangıç yaşı ve birincil enfeksiyon ile HZ arasındaki zaman aralığı, yaşamın ilk yıllarında suçiçeği olan ve hayatının ilk yılından sonra suçiçeği olan çocuklarda değerlendirildi.

Materyal ve Method: Bu retrospektif çalışmada, Temmuz 2012 ile Haziran 2013 tarihleri arasında X Çocuk Enfeksiyon Hastalıkları biriminde takip edilen HZ tanılı 19 çocuk değerlendirildi. Bu çocuklar arasından immün yetersizliği, malignitesi ve diğer immün yetersizlik durumları gibi immünsüpresyonu olan çocuklar çalışmadan çıkarıldı.

Sonuçlar: Çalışma döneminde HZ tanısı alan 19 çocuk değerlendirildi. HZ'li 2 çocuk immünsüpressif durum nedeni ile çalışmadan çıkarıldı. Sonuçda bu çalışmada HZ tanılı 17 sağlıklı çocuk değerlendirildi. Başvurudaki ortanca yaş 9 yıl idi. Olgulardan 8'i yaşamlarının ilk yılında suçiçeği geçirmişti. Bir olgu ise uterin dönemde (32. Gestasyon haftası) VZV maruz kalmıştı. En sık tutulum torasik dermatomda idi (n=9, 52.9%). HZ başlangıç yaşı ortanca değeri, yaşamlarının ilk yılında suçiçeği olan çocuklarda, yaşamlarının ilk yılı sonrasında suçiçeği olan çocuklara göre anlamlı olarak daha düşüktü (sırasıyla; 7.5 yıl, 13.2 yıl, p=0.001). Ayrıca, primer enfeksiyonu ile HZ arasındaki zaman aralığı da yaşamlarının ilk yılında suçiçeği olan çocuklarda anlamlı olarak daha düşüktü (sırasıyla; 80 ay, 131 ay, p=0.003).

Sonuç: Primer VZV enfeksiyonunun zamanı, sağlıklı çocuklarda HZ gelişimi için belirleyici bir risk faktörüdür. Ayrıca, VZV'ye erken maruziyet, HZ'nin daha erken gelişimi ve de primer VZV enfeksiyonu ile HZ arasındaki zaman aralığının daha kısa olması ile ilişkili olabilir.

Anahtar kelimeler: Herpes zoster, sağlıklı, çocuk.

Introduction

Varicella zoster virus (VZV) infection causes two clinically forms of disease. Primary infection with VZV results in varicella. Herpes zoster results from reactivation of latent VZV infection within dorsal root ganglia. This clinically form is characterized by vesicular lesions clustered in the dermatomal distribution of sensory nerves (1). Herpes zoster is unusual during childhood. It can occur any time after primary infection however the incidence rates increase with age, probably owing to the decrease in specific cell mediated immunity (1, 2). HZ is not rare in children with cellular immune deficiency. But, it may be seen in children without immunosuppression (1, 3-5).

Age is the important determining factor for the development of HZ. The primary VZV infection time could be substantial determinant for the development of HZ. Children infected with VZV in utero or early stage of life may be a risk of developing HZ due to a diminished development of immunity to primary infection at this stage (4, 5).

In this paper, 17 healthy children who developed HZ were presented to emphasize epidemiological and clinical features of HZ. In particular, the age at onset of HZ and the time interval between primary infection and HZ were interpreted in children who had been varicella within the first year of life and who had been varicella after the first year of life.

Population and Methods

In this retrospectice study, we evaluated 19 children who was diagnosed with HZ admitted to xxxxxxxxxx, Departments of Pediatrics Infectious Diseases, between July 2012 and June 2013. Clinical and demographic data were recorded. Laboratory data such as complete blood count, lymphocyte subset count, immunoglobulin levels (IgA, IgM, IgG, IgE), human immunodeficiency virus (HIV) antibodies, anti-VZV IgM and IgG results were evaluated. The children with HZ who had immunodeficiency, recent trauma, surgery, malignancy, HIV infection and other immunodeficiency states such as, transplantation or immunosuppressive therapy were excluded the study. In addition, history of the VZV vaccination were evaluated.

SPSS for Windows 19.0 (Inc., USA) was used for statistical analyses. Medians were used to describe variables that were non-normally distributed. The difference between median values are tested by Mann Whitney U test. A value of $p< 0.05$ was considered to be significant.

Results

In the study period, 2 children with HZ who had diagnosed immunodeficiency and 1 children with HZ who had diagnosed leukemia were excluded from the study. As a result, we evaluated 17 healthy children with HZ in this study. The demographic and clinical characteristics of the children were resumed in Table 1. Ten of them were boys (58.8 %). The median age at presentation was 9 years (4-17 years). The median age at exposed to VZV was 13 months. Eight of them had been varicella within the first year of life. One case with HZ had no history of chickenpox. However, it was detected that the mother of this case had chickenpox during 32nd weeks of gestation. None of them had received antiviral treatment at that time.

The most commonly involvement was thoracic dermatome (n=9, 52.9%). Among children, five (29,4%) had lumbar, 2 (11,7%) had cervical, and 1 (5,8%) had sacral involvement. None of them had facial nerve involvement and more than one dermatome involvement.

Pruritus was the most common complaint in children with HZ (n=14, 82.8%). The other complaints at the presentation were pain (n=12, 70.5%) and fever (n=4, 23.5%). Regional enlarged lymph nodes were noted in 3 children (17.6%) at the time of presentation. Post-herpetic neuralgia and post herpetic itching were not observed in any of them. Complications were developed in the 5 (29.4%) of the children. The complications observed were secondary bacterial infection (3 cases, 17.6%), severe ulceration (1 cases, 5.9%) and depigmantation (1 cases, 5.9%).

Intravenous acyclovir was administered to seven children with moderate to severe symptomatic rash. Three adolescents with moderate to severe symptomatic rash received oral valacyclovir. Seven children did not get treatment because of the healing lesions during the first examination (Table 1). The resolution period for cutaneous lesions was between 5 to 14 days.

In children who had been varicella within the first year had lower median age at onset of HZ than children who had been varicella after the first year (respectively, 7.5 years, 13.2 years, p=0.001) (Table 2) (Figure 1). The time interval between primary infection and HZ was 80 months in children who had been varicella in the first year. This was 131 months in children who had been varicella after the first year (Table 2) (Figure 2). This time interval was significantly lower in children who had been varicella within the first year (p=0.003).

Discussion

Age is the substantial determinant for the development of HZ. HZ incidence increased with age (6, 7). The incidence is the lowest in the first 5 years of age (7). In our pediatric study population, the median age at onset of HZ was 9 years.

Previous studies reported that HZ is more common among immunocompromised children, particularly in children with leukemia, lymphoma and HIV infection (3, 8, 9). Primary infection induces specific antibody and specific T cell mediated immunity. When specific T cell-mediated immunity decreased, reactivation of latent infection leads to HZ (2). However, HZ can be seen in otherwise immunocompetent children. In our study group, no immunosupresed case was detected.

Several pediatric case series reported that the substantial determinant for the development of HZ was having primary VZV infection during the first year of life (4, 5, 10). Morever, intrauterin VZV infection during pregnancy may also lead to an increased risk of developing HZ (3-5). This result could be clarified by a diminished development of immunity to VZV at this early age (10). In our study, the median age at exposed to VZV was 13 months. Eight patients of them had been varicella in the first year. Among our patients, 1 case with HZ had no history of varicella. However, the mother of this case had a history of chickenpox during 32nd weeks of gestation.

Early exposure to VZV may be associated with early presentation of HZ and shorter time interval between primary infection and HZ. David TJ *et al*. reported that this time interval was 3.8 years in patients who had been varicella within the first year of life vs. 6.2 years in patients who had been varicella after the first year (11). In another pediatric study, the age at onset of varicella was significantly lower in immunocompetent children than in immunosuppressed subjects with HZ (1.6 years vs. 4.6 years). The interval between varicella and HZ was 6.2 +/- 3.2 years in immunocompetent children (12). In the present study, the median age at onset of HZ and the time interval between primary infection and HZ were lower in children who had been varicella during the the first year of life.

Herpes zoster in healthy children is mildly symptomatic and usually shows a benign course (5). Pain, pruritus, fever, and lymphadenopathy are the most common symptoms in pediatric HZ patients. The most frequent dermatomal involvement is seen in thoracic site (1, 3, 13). Most common complications are bacterial secondary infection, depigmentation and scarring (1, 5, 12, 13). In our patients, pruritus was the most common complaint. Other symptoms during presentation were pain and fever. Associated with the literature the complications were secondary bacterial infection, severe ulceration and depigmentation. Thoracic dermatome was the most affected site.

The incidence of HZ in children is lower after vaccination (14). Weinmann S *et al*. reported vaccinated children had a lower incidence of HZ than in unvaccinated children (15). Universal vaccination programs will probably impact HZ epidemiology in the future, as has happened with varicella. In Turkey, VZV vaccination was added to the Turkish childhood national immunization programme in 2013. Children among the cases reviewed in this paper had not received VZV vaccine.

The goals of antiviral therapy in herpes zoster are to lessen the severity and duration of pain, prevent new lesion formation, rapid healing of lesions and decrease viral shedding to reduce the risk of transmission (16, 17). Acyclovir has been shown to be effective for the treatment of HZ in healthy and immunocompromised patients (1, 18). Famciclovir and valacyclovir are effective oral agents for HZ (1). In this study, antiviral treatment was administered to 10 children with moderate to severe symptomatic rash. However, 7 children did not get treatment because of the healing lesions during the first examination.

Conclusively, HZ in immunocompetent children was found not to be as mild as generally accepted. The time of the primary varicella infection may be indicative to the timing of HZ. Early exposure to VZV may be associated with early presentation of HZ and shorter interval between primary varicella infection and HZ.

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Table 1. Clinical and Demographic Features of the 17 Children with Herpes Zoster

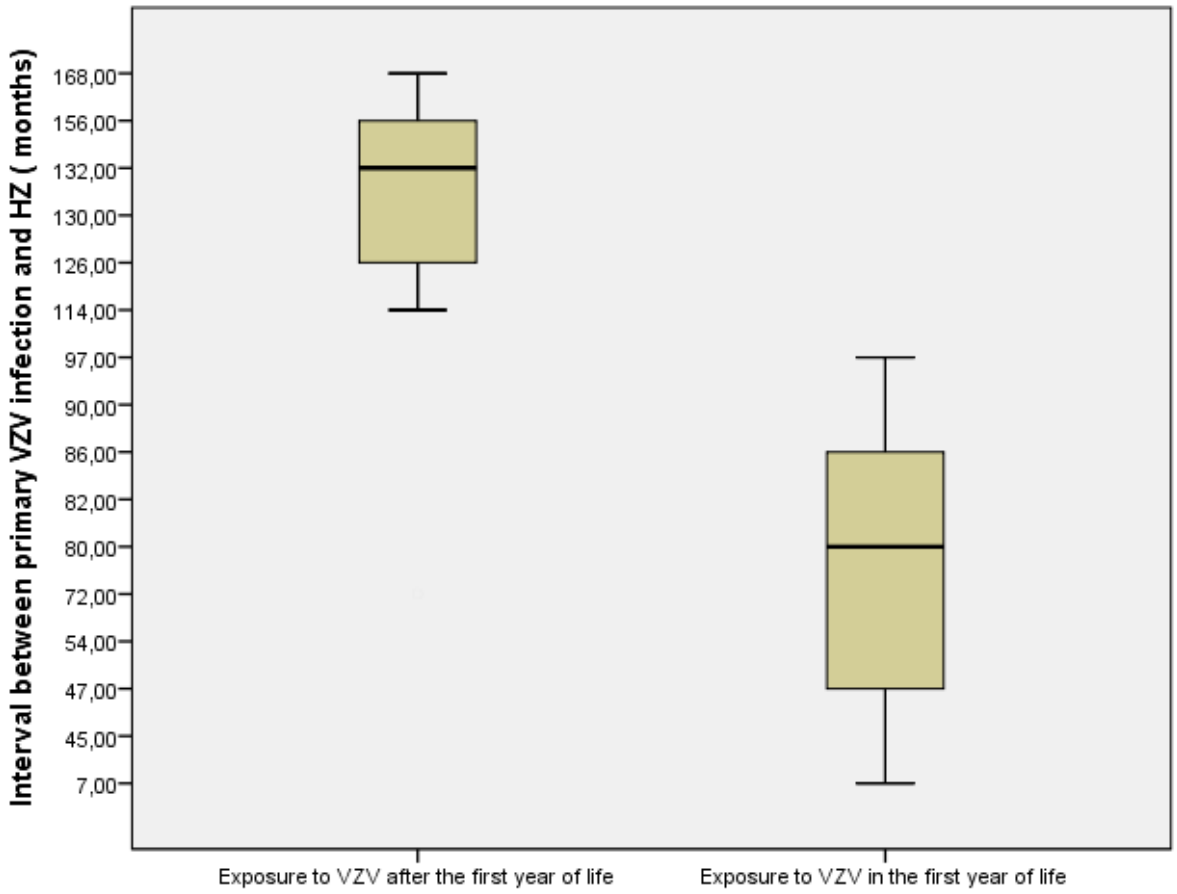
Case Number	Age (years)	Gender	Time of Exposure Primary VZV	Dermatome	Clinical Manifestation	Complications	Treatment/Period of Treatment (days)
1	12	Boy	14 month	Throcic	Rash, pruritus, pain	Depigmentation	Acyclovir (IV)/10 days
2	12,5	Girl	36 month	Throcic	Rash, pruritus, pain	-	Acyclovir (IV) /8 days
3	14	Boy	36 month	Cervical	Rash, enlarged lymph nodes	-	-
4	7,5	Boy	4 month	Lumbar	Rash	-	-
5	9	Girl	36 month	Throcic	Rash, pruritus, fever	Bacterial skin infection	Acyclovir (IV)/10 days
6	7,5	Boy	10 month	Lumbar	Rash, pruritus, pain, fever	-	-
7	8	Girl	6 month	Cervical	Rash, pain	-	-
8	15	Boy	24 month	Throcic	Rash, pruritus, pain	-	Valacyclovir (PO)/7 days
9	17	Boy	36 month	Lumbar	Rash, pruritus, pain, enlarged lymph nodes	-	Valacyclovir (PO) /10 days
10	4	Girl	22 days	Throcic	Rash, pruritus, pain	-	Acyclovir (IV) / 7 days
11	5,5	Boy	12 month	Throcic	Rash, pruritus, pain	-	-
12	7,5	Boy	8 month	Lumbar	Rash, pruritus, pain, fever	Bacterial skin infection	Acyclovir (IV) /8 days
13	9	Girl	11 month	Throcic	Rash, pruritus	-	-
14	12	Boy	18 month	Throcic	Rash, pruritus	-	-
15	15	Girl	48 month	Sacral	Rash, pruritus, pain, enlarged lymph nodes	Bacterial skin infection	Valacyclovir (PO)/8 days
16	4	Boy	3 month	Throcic	Rash, pruritus, pain, fever	Severe ulceration	Acyclovir (IV) /10 days
17	7	Girl	In utero (32 weeks of gestation)	Lumbar	Rash, pruritus, pain	-	Acyclovir (IV) /7 days

Table 2. The onset time of herpes zoster (HZ) and the time interval between primary varicella zoster virus (VZV) infection and HZ in children who had been varicella after the first year of life and who had been varicella in the first year of life .

	Children who had been varicella after the first year of life (n=8)	**Children who had been exposed to VZV in the first year of life (n=9)**	***p*-value**
The onset time of HZ (years)	13.2 (3)years	7.5 (3) years	**0.001**
The interval between primary varicella zoster virus (VZV) infection and HZ (months)	131 (33) months	80 (42) months	**0.003**

Figure 1. The onset time of herpes zoster (HZ) in children who had been varicella after the first year of life and who had been varicella in the first year of life .

Figure 2. The time interval between primary varicella zoster virus (VZV) infection and herpes zoster (HZ) in children who had been varicella after the first year of life and who had been varicella in the first year of life .



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