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Original Article

Menopausal transition may affect the onset of Herpes Zoster: An update on herpes zoster vaccine

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Abstract

Aim: Herpes zoster (HZ) vaccine maintaining routinely aged ≥60 years due to the debated data on long-term effectiveness. We aimed to evaluate age specific incidence of HZ and possible impact of age and gender differences on the onset of disease to contribute age-appropriate vaccination.

Materials and Methods: A total of number 599 patients diagnosed with HZ were evaluated retrospectively. Patients were divided into groups by age. Patients' demographic characteristics, physical examination findings, data of seasonal disease distribution, lesions location, rate of antiviral drug prescription, administered antiviral agent, and presence of accompanying systemic diseases were evaluated.

Results: The 599 patients included in this study were 296 (49,4%) male, 308 (50,6%) female and the mean age of total patients was 50.6±18.84 years. There were statistically significant differences between males and females according to the age groups (p=0,006). In addition, the frequency of disease was significantly increased by age (p=0,000). Moreover, HZ incidence peaked in the fifth decade of life and 64,1% of the patients were aged ≥ 45 years. Furthermore, HZ frequency was significantly higher in males (%67.6) than females (%32.4) in aged between 26 to 35 group (p=0,03) and higher in females (%61.7) than males (%38.3) in 46-55 years age group (p=0,012).

Conclusion: Sudden menopausal hormone alteration in females between 46 to 55 years of age, may cause an increased frequency of HZ. In this respect, despite current recommendations for vaccinating adults, utilization of HZ vaccine particularly in female patients aged above 45 years may be more beneficial in prevention of disease.

Keywords: Herpes zoster; elderly; Vaccination; Varicella Zoster Vaccine; Varicella-Zoster virus

INTRODUCTION

Varicella-Zoster virus (VZV) is a double-stranded DNA virus, which causes varicella (chickenpox) in childhood. Following primary infection, virus becomes latent in dorsal sensorial ganglia and reactivates with typical presentation of herpes zoster (HZ) (shingles) in adulthood. HZ is characterized by vesicules, hyperemia, and pain in relevant dermatomes (1).

The life time probability of HZ (shingles) reactivation is estimated to be 10-30% and the risk considerably increases above 50% in patients aged ≥85 years (2). The reported frequency of complications of HZ ranges from 13% to %40 and post herpetic neuralgia (PHN) is the most commonly documented complication. PHN is documented in approximately 10-20% of all cases and in 30% of elderly cases. Following the acute setting, vesicular rash, severe pain, paresthesia, and dysesthesia may develop in the relevant dermatome (3).

Age is most prominent risk factor in clinical presentation and development of complications. It is well-known that HZ risk increases with age (4). In addition, a live, attenuated chickenpox vaccine was first developed by Dr. Takahashi in the mid-70s and approved in 1995. It is commonly utilized worldwide, thus contributes to decreased morbidity and mortality of the disease (5). Food and Drug Administration (FDA) recommended routine vaccination of patients aged above 60 in 2006. Although in 2011 FDA revised recommendations and approved the use of vaccine among adults aged 50 through 59 years. On the other hand, Centers for Disease Control (CDC) and Advisory Committee on Immunization Practices (ACIP) declined the recommendations, due to the debated complications and limited published data on long-term effectiveness (6). Therefore, we aimed to evaluate the age specific incidence of Herpes Zoster and the possible impact of age and gender differences on the onset of disease to contribute age-appropriate vaccination.

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MATERIALS and METHODS

A total number of 962 patients were evaluated retrospectively. The 599 cases who comply with the scheduled therapy and follow-up procedure were enrolled into the study. The records of patients obtained from Hospital Data Management System (HBYS). Subjects (n=363) with inadequate and missing data related to diagnosis and treatment process were excluded from present study.

Patients were divided into 6 groups by age: < 25 years old, 26 to 35 years old, 36 to 45 years old, 46 to 55 years old, 56 to 65 years old and > 65 years old. Additionally, age of patients was also classified into decades. Patients' demographic characteristics, physical examination findings, the data of seasonal disease distribution, lesions location, antiviral drug prescription, administered antiviral agent, and presence of accompanying systemic diseases were recorded and evaluated.

Statistical Analysis

All the data were analysed with SPSS (Statistical Package for the Social Sciences) software for Windows (v21.0; IBM, Armonk, NY, USA). Individual and aggregate data were summarized using descriptive statistics including mean, standart deviations, medians (min-max), frequency distributions and percentages. Normality of data distribution was verified by Kolmogorov-Smirnov test. Comparison of the variables with normal distribution was made with Student T Test. The variables which were not normally distributed, the Mann Whitney and Kruskal Wallis tests were conducted to compare between groups. Evaluation of categorical variables was performed by Chi-Square test. P-Values of <0.05 were considered statistically significant.

RESULTS

The 599 patients included in this study were 296 (49,4%) male, 308 (50,6%) female and the mean age of total participants was 50.74±18.56 (Ranged: 12-91) years. Although there were no statistically significant differences found between the male (49,23±18.37) and female (52,21±18.66) groups according to the age (p=0,082) in total patients; age groups significantly differed between the male and female groups (p=0,006) (Table 1). Moreover, the frequency of the disease was significantly increased with age (p=0,000). In addition, HZ incidence peaked in the fifth decade of life (Figure 1).

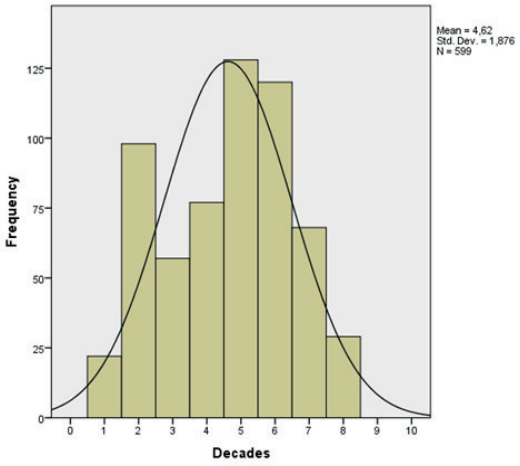

Figure 1. Histogram distributions of the patients according to the decades at the time of diagnosis

In our study, according to the evaluation of disease prevalance between gender and age groups, HZ was found to be significantly more prevalent in males (% 67.6, n=50) than females (%32.4, n=24) in aged between 26 to 35 group(n=74) (p=0,03). Additionally HZ frequency was significantly higher in females (%61.7, n=66) than males (%38.3, n=41) in aged between 46 to 55 group (n=107) (p=0,012). Moreover %25 of patients were aged over 65 years, and 64,1% were ≥ 45 (Table 1) (Figure 2).

The most frequent comorbid disease was diabetes mellitus (10,7%, n=64) in all patients; followed by coronary artery disease (7,0%) and depression (3,8%), respectively (Table 2). Patients most frequently presented in summer with a percentage of 27,5%; followed by spring 27%, winter 23,5% and autumn 22%, respectively (Figure 3).

Table 1. Distributions of the patients according to the age groups and gender

Age Groups	Male n (%)	Female n (%)	Total n (%)	p-value
< 26 years	36 (46.8%)	41 (53.2%)	77 (12.9%)	
26-35 years	50 (67.6%)	24 (32.4%)	74 (12.4%)	
36-45 years	40 (54.1%)	34 (45.9%)	74 (12.4%)	
46-55 years	41 (38.3%)	66 (61.7%)	107 (17.9%)	0.006*
56-65 years	59 (50.4%)	58 (49.6%)	117 (19.5%)	
> 66 years	70 (46.7%)	80 (53.3%)	150 (25.0%)	
Total	296 (49.4%)	303 (50.6%)	599 (100%)	

*= Chi-Square Test= p<0.05 statistically significant

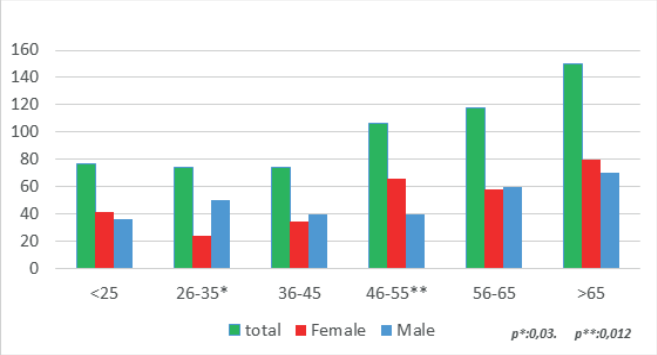

Figure 2. Distributions of the patients according to the age groups and gender

Table 2. Comorbid diseases

Comorbid diseases	n	%
Diabetes mellitus	64	10.7
Coronary artery disease	42	7
Depression	23	3.8
Chronic obstructive pulmonary disease	22	3.7
Rheumatologic disease	19	3.2
Malignancy	8	1.3
Chronic kidney failure	5	0.8
Heart failure	4	0.7
Demantia	4	0.7
Hiv/Aids	3	0.5
Hypothyroidism	2	0.3
Viral hepatitis	2	0.3
Acromegaly	1	0.2

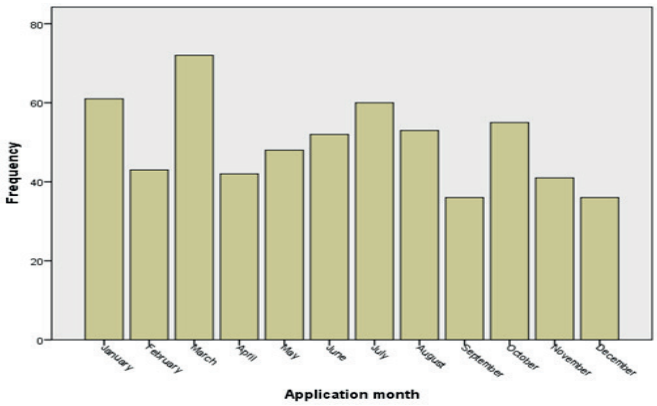

Figure 3. Monthly distribution of HZ cases

There was no statistically significant difference found according to the lesion location between gender groups (p=974). Dermatomes most frequently (48%) localized in thoracic region, followed by cervical 23,7%, lumbar 17%, sacral 8,5% and trigeminal 1,6% respectively

DISCUSSION

Age is the most prominent risk factor on development of HZ. The prevalence of HZ typically increases with older ages (7). Higher prevalence in older ages indicates weakened VZV specific cellular immunity gradually. Supportively, in present study, we also revealed an increased incidence of HZ in older ages. In addition, gender differences in VZV incidence appears to be debated. Lin et al. documented a significantly higher incidence in male gender (8). On the contrary, Fleming et al. reported significant excess in female gender according to the gender-specific age-standardized incidence data. Researchers also documented higher HZ incidence of females in all age groups except for the 15–24 years age group and relatively increased risk of the disease in 45 to 64 years age group for females (9). Another study demonstrated that HZ incidence is more common in male gender for the age group 15 to 24 years and more common in females for all other age groups, thus researchers defined ages between 25 to 64 years as an independent risk factor in females for the HZ infection (10). Both mentioned studies noted that the disease is not more prevalent in females between 15 and 24 years of age. In our study, of the patients 49,4% was male and 50,6% female. Although there were no statistically significant differences found between the male and female groups according to the age (p=0,082) in total patients; age groups significantly differed between the male and female groups (p=0,006). In accordance with published data, no statistically significant difference found according to the gender in 15 to 24 years age group as well. Additionally, Fleming and Wim Opstelten highlighted that the disease is more common in the age groups 45-64 years and 25-64 years in female gender, respectively. Consistently, HZ incidence peaked in the fifth decade of life in our study. Moreover, we demonstrated a significant increased female incidence in the age group 45-55 years. Furthermore, it was also remarkable that HZ incidence in female gender between 56 to 65 years of age was not significantly higher than males despite the patients' older age.

The overwhelming incidence of herpes simplex in females supports the hypothesis that females respond differently than males for latent alpha herpes virus infections (9). In addition, a study showed that contact patients with chickenpox or exposure to VZV may protect previously infected adults against HZ (11). As the young female population makes more contact with children, young women may have a lower incidence of HZ than men. The only age group in our study that the frequency of HZ is higher in males is 26-35 years age group. The reason why males suffer statistically more from the disease only between 26 and 35 years of age, is may be they are more prone to occupational, physical and psychiatric tiredness as well as make less contact with symptomatic children. Similarly, increased number of cases in females of advanced age may be explained by their lower probability of being contact with VZV.

Comorbid diseases, which increases by aging, such as diabetes mellitus, malignancies, and coronary heart disease should be taken into consideration as predisposing factors for the latent viral infection of VZV (10). However,

the HZ cases included into our study was not significantly higher in advanced age groups despite their comorbid diseases. This inconsistency could not be explained by aging or comorbid diseases, it indicates potential effect of hormonal alternation in menopause, which is reported to occur between 45 and 55 years of age in our country (12,13). Moreover, to our knowledge, there is no study available in published data that evaluated the association between menopause and VZV infection. On the other hand, it was documented that humoral and cellular immune responses are weaken after menopause in numerous study. The effect of gender difference on immune function is well-known today. Autoimmune diseases are common in fertile women due to the immune activating effect of estrogen and natural immunosuppressive effect of androgen and progesterone (14). Sex hormones also decrease with aging, correspondingly this causes a decline in immune function (15). In postmenopausal women, the number of CD4 T-lymphocytes along with B-lymphocytes decreases and the cytotoxic activity of natural killer cells decline (14). Consequently, inadequate immune response, invasion of the pathogens and increased sensitivity to infections occur in this age group (15). It was demonstrated in previous studies, postmenopausal women had more recurrence of human papillomavirus (HPV) infections, more frequent urinary system infections and higher risk of heterosexual human immunodeficiency virus (HIV) transmission along with a diminished immune response to some vaccines (16-18). Thus it suggests that sudden hormonal alterations in females between 46 to 55 years of age due to menopause may have unfavorable effects on immune system causing an increased number of our HZ cases.

Immunological debility and advanced age are regarded as risk factors for HZ (19). While the risk is much more higher in immunosuppressive conditions such as HIV infection, myeloma, and lymphoma. Furthermore, there are also other risk factors including rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease (COPD), asthma, chronic renal failure and type 1 diabetes mellitus (type 1 DM) (20). Nevertheless, immunocompetent patients constitute more than 90% of HZ cases (21). Supportively in a study consisting of 1669 adults diagnosed with HZ, Yawn et al. reported that majority of patients (92%) were immunocompetent, 68% of cases were aged >50 years and 60% were women. In addition, researchers concluded that HZ primarily affects immunocompetent adults older than 50 years (22). Similarly in our study, the rate of immunosuppressive cases was found as low as 2,6%.

The most common comorbid disease in a retrospective study, included 34280 patients and conducted by Jaw-Shyang JIH et al.,was diabetes mellitus, and followed by leukemia-lymphoma, breast cancer, liver cancer, systemic lupus erythematosus (SLE) and HIV/AIDS, respectively (23). In another study has documented accompanying disorders as DM, COPD, malignancies and rheumatological diseases, respectively (10). In accordance with these published data, the most frequent comorbid disease wasdiabetes mellitus in our patients as well.

There are numerous published studies which evaluated the relation of HZ with seasonal conditions. In addition, several data suggesting unfavorable effects of UV light on the immune system by several mechanisms are available, though these are not fully clarified. Thus, sunlight and high temperature are thought to cause latent virus reactivation theoretically (24). In a retrospective study, HZ cases were found to be mildly increased in summer and autumn (25). Similarly, Ho Soon et al. documented higher frequency of cases in spring and summer than in winter (26). On the contrary, Kosuke reported no significant seasonal influence on HZ (27). Consistently with majority of published data, HZ frequency was peakedin spring and summer in present study.

HZ is characterized by lesions localized unilaterally within the midline and mostly emerged as thoracic dermatomes. The other most commonly involved territory of dermatomes are documented to be vary in published data (28). Lumbar, cranial (trigeminal) and cervical dermatomes have been mentioned as the second most common region in different studies (29). In accordance with these data, in our patients dermatomes most frequently (48%) localized in thoracic region, followed by cervical 23,7%, lumbar 17%, sacral 8,5% and trigeminal 1,6% respectively.

CONCLUSION

In conclusion, although current recommendations for vaccinating adults, our findings indicate that utilization of Herpes zoster vaccine particularly in female patients aged above 45 years may be more beneficial in management of disease. In this respect further researches, which particularly associated with potential effect of menopausal hormone changes on VZV infection, should be perform to contribute the update of vaccination guidelines and management of HZ.

Competing Interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical Approval: Fatih Sultan Mehmet Training and Research Hospital, Clinical Research Ethic Committee approved the study. Approval date and number: 20/04/2017, 531.

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