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Risk factors in patients with herpes zoster infections: case-control study

Research Article

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Abstract: The aim of this study was to determine the prevalence of chronic disease and the risk factors for herpes zoster infection. In this case-control study medical records were collected from 55 patients who presented with herpes zoster and 54 patients in a control group who presented with gastroenterocolitis. Both groups were treated at the Clinic for Infectious Diseases, University Clinical Hospital Mostar from January, 2005 to December, 2010. When we compared the herpes zoster group with the control group, we did not demonstrate any significant difference in the overall prevalence of chronic diseases. However, the prevalence of diabetes and cancer was statistically higher when compared to the control group. A statistically significant difference in the number of cigarette smokers was not observed, whereas the number who consumed alcohol in the herpes zoster group was significantly higher compared to the control group. The correlation between alcohol and herpes zoster could help in solving the reactivation mechanism of VZV.

Keywords: *Varicella-zoster virus • Herpes zoster • Prevalence • Risk factors • Chronic diseases • Alcoholism*

1. Introduction

Varicella-zoster virus (VZV) is classified in the family Herpesviridae in the subfamily Alphaherpesvirinae [1]. It causes two epidemiologically and clinically different diseases: chickenpox (varicella) and herpes zoster (shingles). Varicella is acute primary VZV infection, and it is characterized by fever, headache, myalgias and exanthems with a vesicular eruption of the skin. In children, varicella is a common self-limiting disease occurring in annual spring epidemics [2]. However, varicella infection in neonates, adults and immunosuppressed patients can lead to severe complications such as encephalitis and pneumonitis [3-4]. Herpes zoster results from reactivation of latent VZV infection in the dorsal root of spinal ganglia and in the ganglia of certain cranial nerves. The mechanism of reactivation is not yet fully understood. It is believed that the reactivation is due to the reduction of VZV-specific cellular immunity, and thus periodic exposure to persons with varicella or herpes zoster may enhance VZV-specific cellular immunity characterized by periodic subclinical reactivation of the virus [5].

Herpes zoster, unlike varicella, occurs predominantly in the elderly, and its appearance has no epidemic character. Many studies have shown that herpes zoster exhibits no seasonal pattern [6], whereas others have shown a higher incidence in the warmer part of the year, as a consequence of increased exposure to ultraviolet (UV) light [7]. Clinically, it is manifested by a unilateral vesicular rash in the area of a dermatome supplied by the ganglia with latent VZV infection. The prodromal stage usually occurs 24–48 hours before the eruption of the rash, characterized by fever, malaise, headache, pain and numbness and tingling in the area of the affected sensory nerve. After the prodromal stage, maculopapular changes appear in erythematous and

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edematous skin over 3–5 days, followed by the development of vesicles. The rash heals in 2–4 weeks [3]. The most frequent localization of the dermatomal rash is the thoracic nerves and ophthalmic division of the trigeminal nerve (herpes zoster ophthalmicus) [8].

Complications develop in nearly 50% of adults presented with herpes zoster [4,9]. The most common complication is postherpetic neuralgia (PHN), a neuropathic pain syndrome that persists or develops 1 or more months after the dermatomal rash has healed [10]. The main risk for PHN is aging. PHN occurs in 36.6% of patients more than 60 years of age and in 47.5% of those more than 70 years [4]. Other risk factors that include severity of acute zoster pain and rash are painful onset of disease and ocular involvement. Patients with PHN usually describe the sharp pain followed by burning and aching in the region that corresponds with the earlier rash [10]. Other rare complications include encephalitis, myelitis, retinitis and paresis [8].

The incidence of herpes zoster increases with age. The disease develops in approximately 20–30% of the general population during their lifetime and in 50% of the population more than 85 years old [4]. The incidence of herpes zoster in children under 10 years is 0.25–1.15/1000 and 0.43–1.60/1000 in adolescents [11], whereas the incidence of herpes zoster in adults is 3.6–14.2/1000 [12].

The diagnosis of herpes zoster is based on the clinical signs and symptoms. Therefore, it is rarely necessary to establish the etiologic diagnosis of herpes zoster either by VZV-DNA isolation from vesicles or from blood, followed by polymerase chain reaction (PCR), or serological evidence of the fourfold rise in titer of specific antibodies with use of the enzyme-linked immunosorbent assay (ELISA) technique [13].

For the treatment of herpes zoster, acyclovir is the drug of choice and should be applied within 72 hours of the rash appearance. It has been shown that acyclovir treatment speeds the healing of the rash to within 1–2 days and also relieves acute pain [8,14], but it does not prevent the occurrence of PHN [8,15-16]. In addition, treatment with both acyclovir and corticosteroids has the same effect as treatment with acyclovir only [8,14,17]. Opioids and some antiepileptic drugs (e.g., gabapentin) are used to relieve acute pain, whereas tricyclic antidepressants are used for the prevention of PHN [8,18].

Herpes zoster is associated with a number of risk factors, the most important of which are age, gender, race and ethnicity or certain chronic diseases.The incidence of herpes zoster is significantly increased with age, affecting 50% of the population older than 85 years [6,19]. A greater incidence of herpes zoster was shown in women [11,12]. Black race is associated with a risk of the development of herpes zoster that is four times lower than that of other races, due to differences in VZV-specific cellular immunity [20]. Although it has been speculated that the socio-economic status, place of residence (urban compared to rural areas) and stress could contribute to the development of herpes zoster, the review by Thomas and Hall excluded those as potential risk factors for herpes zoster infection [12]. Altogether, the high-risk groups for the incidence of herpes zoster are patients with cancers, HIV infection, autoimmune diseases, hypertension, diabetes mellitus and some other chronic diseases [12,21,22]. Persons who are HIV-positive have a risk 12–17 times higher for the development of herpes zoster [2]. Patients who have undergone allogeneic or autologous bone marrow transplantation also have a higher risk of herpes zoster; the risk is highest immediately after transplantation [23].

2. Methods

2.1. Place and time of the study

The study was conducted at the Clinic for Infectious Diseases of the University Clinical Hospital (UCH) Mostar from January, 1st 2005 to October, 31st 2010.

2.2. Subjects and study parameters

The study included 55 patients who presented with herpes zoster. Since the syndrome of acute gastroenterocolitis (GEC) does not generally depend on comorbidity, we included 54 patients who presented with GEC as a control group. All subjects in the control group tested negative on microbiological stool analysis.

The data were collected by reviewing the medical records. The herpes zoster group was matched with the control group by age and sex, with a maximum deviation of the median age by 2 years.

The independent variables were age, gender, employment status, lifestyle habits (smoking, alcohol), place of residence, chronic diseases (e.g., diabetes mellitus, arterial hypertension, autoimmune diseases and cancer) and incidence of impetiginization (occurrence of impetigo) as complications of the disease. The dependent parameter was the prevalence of chronic disease in patients with herpes zoster.

3. Statistical analysis

For comparison of nominal variables, a $\chi 2$ test was used. Due to the lack of the expected frequency, the Fisher

exact test was used for comparison of the categorical variables, except in the case of comparing dichotomous variables, when Yates correction was used.

The possibility of error was accepted at α <0.05, and differences between groups were accepted as statistically significant at *P* <0.05.

For statistical analysis, the SPSS software system for Windows (version 13.0, SPSS Inc., Chicago, Illinois, USA) and Microsoft Excel (Version 11, Microsoft Corporation, Redmond, WA, USA) were used.

4. Results

In this study, we observed a similar incidence of herpes zoster with respect to the gender of the patients. Of the total patients with herpes zoster, 29 (52.7%) were male and 26 (47.3%) were female (χ^2 test=0.16; s.s.=1; *P*=0.686). We showed that the incidence of herpes zoster increased with age. The oldest age group was the most common, representing 54.5% of all patients (χ^2 test=13.53; s.s.=2; *P*=0.001) (Figure 1).

After comparing the incidence of herpes zoster in patients from urban areas (28, or 50.9%) and those from rural areas (27, or 49.1%), we did not observe a statistically significant difference between these groups (χ^2 test=0.02; s.s.=1; *P*=0.893).

Although we observed that herpes zoster appears more frequently in spring and summer than in autumn and winter, this difference was not statistically significant (χ^2 test=7.18; s.s.=3; *P*=0.066).

In this study we showed a higher prevalence of alcohol consumption in the group with herpes zoster, as compared to the control group with gastroenterocolitis (χ2 test=5.45; s.s.=1; P=0.020) (Figure 2). However, our study showed no statistically significant difference in the prevalence of cigarette smokers between the two groups (χ2 test=0.19; s.s.=1; P=0.661).

In 24 (43.6%) of the total patients with herpes zoster, complications occurred in the form of impetiginization (χ^2 test=0.89; s.s.=1; *P*=0.345). In addition, the highest incidence of complications in the form of impetiginization was observed in the oldest group of herpes zoster patients (χ^2 test=14.49; s.s.=1; *P*=0.001).

We did not find a statistically significant difference in the prevalence of overall chronic disease (χ^2 test=0.75; s.s.=1; *P*=0.385), and neither did we find a significant difference in the prevalence of arterial hypertension between the herpes zoster and control groups (χ^2 test=0.23; s.s.=1; *P*=0.630). However, we noted a

Figure 1. The incidence of herpes zoster based on the age of the patients presented with herpes zoster, the Clinic for Infectious Diseases UCH Mostar in the period from January, 1st 2005 to October, 31st 2010.

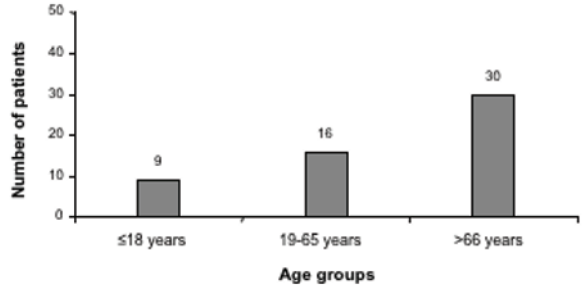


Figure 2. Comparison of herpes zoster and control group in the frequency of herpes zoster due to the alcohol consumption, the Clinic for Infectious Diseases UCH Mostar in the period from January, 1st 2005 to December, 31st 2010. (HZ–Herpes zoster, GEC–gastroenterocolitis).

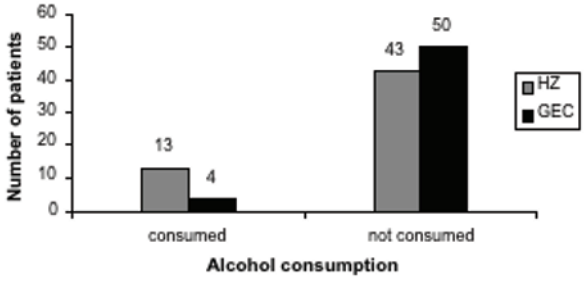


Figure 3. The prevalence of diabetes mellitus in the herpes zoster and control group, the Clinic for Infectious Diseases UCH Mostar in the period from January, 1st 2005 to December, 31st 2010. (HZ–Herpes zoster, GEC–gastroenterocolitis).

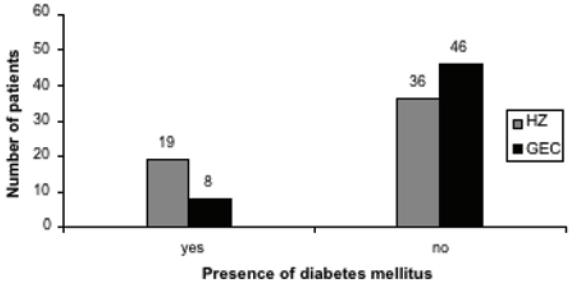
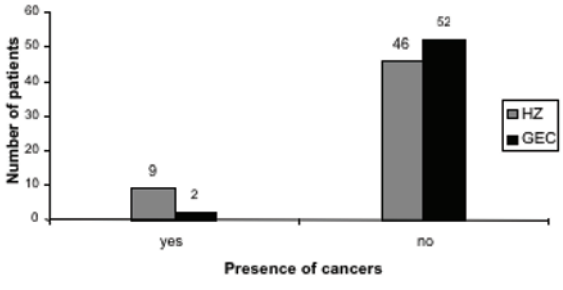


Figure 4. The prevalence of cancers in the herpes zoster and control group, the Clinic for Infectious Diseases UCH Mostar in the period from January, 1st 2005 to December, 31st 2010. (HZ–Herpes zoster, GEC – gastroenterocolitis).



significant difference in the prevalence of diabetes mellitus between the herpes zoster and control group (χ^2 test=5.69; s.s.=1; *P*=0.017) (Figure 3).

Also, we found a statistically significant difference in the prevalence of cancer between the two groups (χ^2 test=4.81; s.s.=1; *P*=0.028) (Figure 4). However, we did not find a statistically significant difference in the prevalence of autoimmune diseases (χ^2test=0.16; s.s.=1; *P*=0.691; Yates correction). Moreover, there was no statistically significant difference in the prevalence of other chronic diseases (e.g., chronic obstructive pulmonary disease, bronchial asthma and cardiomyopathy) between these groups of patients (χ^2 test=0.04; s.s.=1; *P*=0.835)

5. Discussion

In this study we showed a statistically significant prevalence of diabetes mellitus and cancer in patients with herpes zoster, as compared to a control group of patients with gastroenterocolitis. Although we observed a higher prevalence of overall chronic disease in patients with herpes zoster (67.3%), the overall prevalence was not statistically significant in comparison to the control group (59.3%), which is in opposition to previously published data [12,21,22]. A possible explanation for this discrepancy could be the lower number of patients in our study, as compared to studies conducted in England and Wales, where more than 502,493 patients were followed over a multi-year period [12]. On the other hand, our systematic approach performed with a valid control group clearly indicates the presence of chronic diseases in both the herpes zoster and the control groups. The results obtained in this study clearly demonstrate that hypertension (50.9%) and diabetes mellitus (34.5%) were the most common chronic diseases in the study group. However, unlike hypertension, the prevalence of diabetes mellitus was significantly higher in patients with herpes zoster in comparison to the control group. An increased prevalence of diabetes mellitus in herpes zoster is in accord with the results of a study performed on 63 subjects with diabetes mellitus and 67 healthy subjects in Japan [21]. In accordance with previously published data, our data showed a statistically significant prevalence of cancer (16.4%) in patients with herpes zoster, while the prevalence of autoimmune diseases (7.3%) was not related to a higher incidence of herpes zoster [12,22]. Furthermore, a study performed in the United States of America showed that after 5 years of treatment, the incidence of herpes zoster in patients with Hodgkin's lymphoma was 14%, in patients with non-Hodgkin's lymphoma 10%, and in patients with breast or lung cancer 2%, suggesting that patients with lymphoproliferative cancer have a higher risk of herpes zoster compared to other malignancies [2]. In contrast to the American study, we found an incidence of herpes zoster in patients with prostate cancer (3 of 9 patients; 33%) similar to that in patients with lymphoproliferative disorders (2 of 9 patients; 22%). However, it should be taken into account that most of the patients with lymphoproliferative disorders were treated in other referent Centers for Hematology in our country, as well as neighboring countries. Therefore, this could be why we did not observe the highest prevalence of lymphoproliferative disorders among patients with cancer and herpes zoster infection.

A possible reason for the higher risk for herpes zoster in patients with chronic diseases is immunosuppression, particularly the suppression of cellular immunity. Immunosuppression in patients with diabetes mellitus is an integral part of the disease, and thus, these patients are at high risk for the development not only of herpes zoster, but also other infections. Unlike diabetes mellitus, immunosuppression caused by treatment with chemotherapeutics in patients with autoimmune disease and cancer increases the risk of herpes zoster [1,2,5,21-23].

In agreement with previously published data, our study showed that the incidence of herpes zoster increases with the age of patients [1,2,8,9,12,19,24]. Specifically, the highest incidence of herpes zoster was observed in patients older than 66 years (54.5%), as compared to patients younger than 18 years (16.4%). The observed differences are most likely a consequence of impaired cellular immunity and a higher incidence of chronic diseases in the elderly, who are themselves in the high-risk group for herpes zoster [2]. When this was taken into account, the incidence of impetiginization was higher in the elderly patients with herpes zoster. However, the frequency of impetiginization in patients with herpes zoster was not dependent on the presence of diabetes mellitus. Consistent with previous work, we did not observe an association of the frequency of herpes zoster with seasonal prevalence in the warmer part of the year and place of residence [12]. The higher incidence of herpes zoster in the warmer parts of the world could be a consequence of proven harmful effects of ultraviolet radiation (UV radiation) on cellular immunity [2]. Furthermore, we did not observe a statistically significant difference in the gender of patients with herpes zoster. Contrary to previously published data, our results showed an equal prevalence of herpes zoster in both men (46.7%) and women (53.3%) [12,24]. Of the 11 studies conducted world-wide, only 4 demonstrated a higher incidence of herpes zoster in women, while in the other studies herpes zoster was similarly distributed

between men and women [12]. So far, there is no explanation for possible differences in the incidence of herpes zoster between the sexes. It might be that there are differences in the biological mechanisms of herpes zoster reactivation, or there is a greater prevalence of other risk factors for the development of herpes zoster in females. However, if we consider the fact that occasional exposure to chickenpox may have a protective immunological role, with a consequent reduction of the risk of reactivation of herpes zoster, then there should be a lower incidence of herpes zoster in women because of their frequent social contact with children [2,12,24]. Taking into account the results of these studies, it remains an unsolved question whether the incidence of herpes zoster could be related to gender and whether there is a possibility of the influence of various hormonal events in the human body, especially in females. Regarding the habits of patients with herpes zoster, our results showed no statistically significant differences with respect to the proportion of smokers, as compared to the control group. However, we found a significantly higher incidence of herpes zoster in patients who consumed alcohol. These data are also interesting from an immunological aspect, because immunosuppressive effects of alcohol might affect the reactivation of latent VZV [2,12]. Bearing in mind the harmful effects of smoking and alcohol, as well as growing number of smokers and alcohol consumers, the impact of those factors on the reactivation of herpes zoster should be explored in the near future.

Further research on this topic should include a larger group of patients during a longer period of time. Despite previous research on risk factors for herpes zoster, we still have a limited knowledge of them and the mechanisms for the reactivation of herpes zoster. In a recent study, Joesoef et al. showed that risks for herpes zoster infection may not contribute substantially to the burden of the disease in the population and most causes of herpes zoster still remain unknown [25]. Therefore, to reduce the incidence of herpes zoster, additional research into risk factors is required. In addition, implementation of new therapeutic approaches for the treatment of chronic diseases such as diabetes mellitus and autoimmune diseases should greatly help in reducing the incidence of herpes zoster. Bearing in mind that extension of the human life span will result in a greater incidence of herpes zoster, especially in poorer areas of the world, studies highlighting the pathogenesis of VZV reactivation are of high importance for the implementation of adequate measures of prevention.

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