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Association between Family History and Herpes Zoster: A Case-Control Study

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ABSTRACT

Background: There are many risk factors besides age and immune suppression for herpes zoster. Family history as a risk factor is suggested in some recent studies. The aim of this study was to evaluate the association between herpes zoster and family history.

Methods: This case-control study was undertaken in Farshchian Hospital, Hamadan, Iran. “Case group” included patients with confirmed diagnosis of herpes zoster. “Control group” was chosen among other dermatologic patients or their companions without any history of herpes zoster. Immune deficiency was the main excluding criteria. Information about age, gender, dermatome involved (only in patient group), history of chronic dermatologic or systemic diseases, and family history of herpes zoster was asked using special questionnaires.

Results: Case and control groups included 217 and 200 participants respectively. Mean age of cases and controls was 49.08±15.59 and 49.96±15.54 years old respectively (*P*=0.936). 53.5% of cases and 54.5% of controls were women (*P*=0.845). Most frequent dermatomes involved in patients were thoracic (85/217; 39.25%) and cervical dermatomes (55/217; 25.3%). Frequency of herpes zoster in first-degree blood relatives in cases and controls was 65/217 (30%) and 16/200 (8%) respectively (OR=4.91; 95% CI: 2.73, 8.85; *P*=0.001).

Conclusions: Our findings indicated a significantly higher proportion of patients with family history of herpes zoster comparing to controls. This study confirms family history as a risk factor for herpes zoster. Therefore, the old patients with positive family history of herpes zoster may be appropriate candidates for vaccination with Zostavax. However, more evidence based on large cohort studies in needed to confirm our findings.

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Introduction

Herpes zoster is a viral disease caused by reactivation of latent varicella zoster virus residing in the dorsal root ganglia. Reactivation of virus is due to factors such as stresses, fever, radiation therapy, tissue damage or immune suppression. Disease occurs in 20% of healthy adults and 50% of immune suppressed patients[1].

Lifetime risk of herpes zoster is estimated to be about 30%, and this means that one in every three people may experience herpes zoster in their life[2]. Incidence and severity of disease increases markedly with age, as in individuals more than 85 years old 50% experience at least one episode of the disease in their life[3,4].

Herpes zoster causes remarkable morbidity and complications such as post-herpetic neuralgia, facial nerve palsy and ophthalmic nerve involvement, which result in considerable costs for management and treatment. Risk of developing post-herpetic neuralgia is 10-18% and for ophthalmic involvement is 10-25%. According to high incidence of the disease, costs for managing and treatment of the patients would be too high[5].

Herpes zoster typically presents with a characteristic painful, localized, vesicular eruption confined to a dermatome[6].Diagnosis of herpes zoster is based on its characteristic clinical presentation. Based on epidemiologic studies self-report of herpes zoster by patients is comparable to physician's examination and diagnosis, and there is no significant difference between these two conditions in regard to accuracy and rate of false positive or negative. Therefore, we can rely on patients` self-report as an accurate source of information[7].

Several factors are discussed as predisposing or risk factors of varicella zoster reactivation. Advancing age and immune suppression are two factors fully elucidated as definite risk factors, but there are many other factors not agreed as precise determinants in herpes zoster[8].

On the other hand, FDA approved a new vaccine specially introduced for herpes zoster named Zostavax since 2006, to be used for people more than 60 years old to prevent herpes zoster and its complications[9]. Zostavax can prevent the incidence of herpes zoster by 50% and post-herpetic neuralgia by 67%[10]. Evaluating risk factors of herpes zoster is important from two points of view: first, efficiency and approval of herpes zoster vaccine can help to prevent this disease and its complications, and second, define risk factors can help to nominate appropriate candidates for vaccination.

Family history is a risk factor suggested in some recent studies. This study was done to assess family history as a risk factor of herpes zoster. The aim of this study was to evaluate the association between herpes zoster and family history, and finding appropriate at risk candidates to introduce for vaccination.

Methods

This case-control study was undertaken in Farshchian Hospital, Hamadan; the west of Iran, from February 2009 to December 2011. Case group included patients with confirmed clinical diagnosis of herpes zoster. Controls were chosen among other minor or chronic dermatologic patients or their companions from the same center. We ruled out history of herpes zoster in participants of control group using the questionnaire shown in Table 1. Patients or controls suspected to have any form of immune deficiency were excluded. The distribution of the covariates is the same among two groups (case & control group) concerning age, gender and not having immune deficiency. Similarly individuals having long term or professional contact with patients (e.g. healthcare workers) were excluded of the study.

Table 1: Questions to rule out history of herpes zoster in controls

1.	Did you ever have red, painful and blistering lesions localized on one side of your body?
2.	Do you remember a diagnosis of zoster, zona or shingles made by your physician anytime in your life?
3.	Is there any pigmentation or scar on your body because of a previous painful, red, painful and blistering skin lesion?
4.	Do you remember any drug name like acyclovir, famcyclovir, penciclovir or so, for a previous skin lesion prescribed by your physician?
5.	Do you remember any red and blistering skin lesion which improved in about 10 days but had a residual pain for some time longer?

Immune deficiency was the most important excluding criteria in both groups. So, participants were asked about immune suppressant drugs (steroid, cyclosporine, cyclophosphamide, methotrexate, chemotherapeutic agents, etc.) and situations (cancer, HIV/AIDS, organ transplant, etc.). Individuals suspected to have memory or neuropsychiatric disorders were excluded of both groups because of unreliable information.

Information about age, gender, dermatome involved (only in patient group), and history of chronic dermatologic or non-immune systemic diseases was attained using a questionnaire within a direct interview session.

Family history of herpes zoster was asked using a special questionnaire; first-degree blood relatives included parents, siblings and children. Second degree blood relatives were grandparents, aunts, uncles and their first children (Table 2).

Table 2: Questions about family history of herpes zoster

1.	Do you remember any of your relatives to have red, painful and blistering lesions localized on one side of the body?
2.	Do you remember a diagnosis of zoster, zona or shingles made by a physician anytime for any of your relatives?
3.	Is there any pigmentation or scar on any of your relatives' body because of a previous painful, red, painful and blistering skin lesion?
4.	Do you remember any drug named like acyclovir, famcyclovir, penciclovir or so, for any of your relatives prescribed by his/her physician?
5.	Do you remember any red and blistering skin lesion which improved in about 10 days but had a residual pain for some time longer any of your relatives?

Diagnosis of patients and selecting participants of control group was conducted by two expert dermatologists. However, two trained investigators who were blinded to cases and controls and purpose of the study did asking the questionnaire and interviews at the first visit. In addition, a blinded statistician analyzed data obtained by these investigators. Data was analyzed using SPSS software version 17.0 (PASW Statistics 17.0.3, IBM Inc.). The *t*-test was used for continuous quantitative variables, and chi-square test and odds ratio (OR) with 95% confidence interval was used for discrete qualitative variables to compare two groups.

Results

Overall, 449 people enrolled in the study, but 9 of the cases and 4 of controls were excluded because of underlying immune suppression. Furthermore, 8 of cases and 11 of controls were excluded because of conflicting information or unreliable memory recovery. Ultimately 217 confirmed patients with herpes zoster and 200 individuals without herpes zoster history in their life were included in case and control groups respectively.

The distribution of the covariates was the same among controls and cases, and there were no significant differences between two groups concerning age, gender and immune deficiency. Data on distribution of age, sex and diseases history in case and controls are shown in Table 3. Frequency of dermatomes involved in patients was 85/217(39.25) for thoracic dermatome, 55/217 (25.3%) for cervical, 34/217(15.7%) for ophthalmic, 33/217 (14.7%) for lumbar, 11/217(5.1%) for limbs.

Table 3: Distribution of age, sex and diseases history in cases and controls groups

	Cases n=217		Controls n=200		
Variables	**Number**	**Percent**	**Number**	**Percent**	***P* value**
Age groups (yr)					0.998
0-20	8	3.7	6	3.0	
21-30	23	10.6	20	10.0	
31-40	34	15.7	31	15.5	
41-50	49	22.6	49	24.5	
51-60	54	24.9	48	24.0	
61-70	29	13.4	26	13.0	
>70	20	9.2	20	10.0	
Gender					0.845
Females	116	53.5	109	54.5	
Males	101	46.5	91	45.5	
History of chronic systemic disease	54	23.5	47	23.5	0.819
History of chronic dermatologic disease	3	1.4	30	15.0	0.001

Absolute number of patients with herpes zoster and family history herpes zoster was 101 and absolute number of the control with family history of herpes zoster was 24.

Positive family history of herpes zoster was significantly more frequent in patient group than controls (*P*=0.001). Frequencies for first degree, second degree and at least one relative were respectively 30%, 16.6% and 46.6%.

Patients had significantly higher proportion of positive family history for herpes zoster in their blood relatives comparing to controls. Likelihood of positive family history in first-degree blood relatives in patients was 4.91 times higher than cases. Furthermore, for second-degree relatives, patients were 4.77 times more likely to have a positive family history. Likelihood to have at least one relative (first or second degree) with positive herpes zoster history was 6.26

times more in patients than in controls. OR for positive history in more than one relative (multiple vs. single) did not suggest a higher risk effect in regard to increasing number of affected relatives.

Data on distribution of family history in case and controls are shown in Table 4.

Table 4: Distribution of family history of herpes zoster in cases and controls

Variables	Cases (n=2017)	Controls (n=200)	OR (95% CI)	*P* value
1st degree relative				0.001
Negative	152	184	1.00	
Positive	65	16	4.91 (2.73, 8.85)	
2nd degree relative				0.001
Negative	181	192	1.00	
Positive	36	8	4.77 (2.16, 10.54)	
Total relatives (1st and 2nd)				0.001
Negative	117	176	1.00	
Positive	100	24	6.26 (3.79,10.36)	
Number of relatives				0.001
0	117	176	1.00	
1	88	24	5.52 (3.32,9.17)	

Discussion

There are many risk or predisposing factors suggested for reactivation of varicella zoster virus. Age and cell mediated immune deficiency are agreed risk factors, whereas several others such as diabetes mellitus[11], female gender[12], genetic susceptibility[12], mechanical trauma, recent severe psychological stress, and white race[13] are suggested and being evaluated in recent investigations. Some of recent studies focused on genetic susceptibility or family history as risk factors for herpes zoster.

First, Hanpaa and colleagues[14] reported that polymorphism in interleukin 10 (IL-10) gene is associated with susceptibility to herpes zoster, and herpes zoster patients are more likely to carry ATA haplotype. ATA haplotype in IL-10 gene results in lowering the production of interleukin 10, which is suspected to have role in reactivation of varicella zoster and causing herpes zoster.

Another genetic study done by Cho JW et al.[15] on Korean population indicated that polymorphism in IL-10 promoter gene especially 1082 allele and GCC haplotype resulted in more susceptibility to herpes zoster. Study on several HLAs indicated that incidence of certain HLAs may result in more susceptibility or more resistance against some infections such as leprosy, HIV and hepatitis[16,17]. According to suggested role of genetic susceptibility in other infectious or viral diseases, we can postulate a similar role in the pathogenesis of herpes zoster.

There are three similar studies suggesting family history as a risk factor for herpes zoster; Hicks et al.[18] suggested family history as a risk factor for herpes zoster in 2008, and then Hernandez et al[19] confirmed stronger correlation between family history and herpes zoster in 2011- in the era of shingles vaccination. In addition, the study of Lasserre et al. in 2012 confirmed that family history increase the risk of occurrence of herpes zoster[20].

Comparing to Hicks et al[18]study, our findings indicate a stronger correlation between family history and herpes zoster, because we found positive family history in 46.6% of our patients compared to 39.3% in Hikcs` study (OR=4.09; 95% CI: 3.06, 5.47).

Hernandez et al[19]reported positive family history in 43.5% of patient group blood relatives (OR=6.55; 95% CI: 2.73, 8.85). We found similar correlation between herpes zoster and family history comparing our findings to Hernandez.

On the other hand, to evaluate dose-dependent effect with increasing number of positive relatives, we used OR for single versus multiple relatives involved (OR=0.786; 95% CI: 0.332, 9.17). Our findings indicated that increasing number of relatives with positive history of herpes zoster, was not associated to higher risk of herpes zoster and our study did not confirm a dose-dependent effect with increasing number of relatives, whereas both studies by Hicks et al. and Hernandez et al. confirmed dose-dependent effect.

There are other studies disputing family history as a risk factor for herpes zoster. In a case-control study on post-herpetic neuralgia patients, Gatti et al [21] reported a lower family history in PHN group than in case group (28.4% vs 29.4%), although we can explain this dissimilarity pointing to that Gatti's patients had post-herpetic neuralgia, not patients suffering acute herpes zoster.

The most important limitation in our study was suspected recall bias. This bias was more probable in controls; because controls did not have an experience of herpes zoster lesions. Instead, patients may over-report their situation. To resolve this problem or to confine the bias effect we asked two members of one family separately but in one session, it means that we asked one participant plus one of his/her first degree relative separately but with one questionnaire, and excluded those with conflicting information. Meanwhile considerable difference between cases and controls lowers the probability of bias in our findings. Furthermore, blinded investigators and statistician improved the accuracy of our study. Another limitation of our study was lower number of cases & controls comparing to similar studies (Hicks and Hernandez).

As mentioned above a special vaccine for herpes zoster (Zostavax) is approved by FDA and available for preventing herpes zoster. Therefore selecting indicated cases to receive this vaccine is the topic of many investigations. Evaluating the suggested risk factors or determinants for herpes zoster can present the indicated candidates for vaccination.

Conclusions

In conclusion, with regard to findings of this study we can suggest family history as a strong determinant or risk factor of herpes zoster infection and candidate individuals with positive family history for prophylactic vaccination with Zostavax. Also larger prospective cohort studies with different geographical areas are needed.

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Conflict of interest statement

The authors have nothing to declare.

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